Form Approved
OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HU... SERVICES
PUBLIC HEALTH SERVI...

GRANT APPLICATI...

FOLLOW INSTRUCTIONS

LEAVE BLANK

NAME: ROSS, RONALD K
APPL NO: 1 R01 CA43092-01
IRG: EDC 2

COUN DATE: 05/86
DATE RECD: 11/01/85

1. TITLE OF APPLICATION *(Do not exceed 56 typewriter spaces)*
A COHORT STUDY OF DIETARY FACTORS IN THE ETIOLOGY OF CANCER IN SHANGHAI.

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT ☒ NO ☐ YES *(If "YES," state RFA number and/or announcement title)*

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME *(Last, first, middle)*
ROSS, Ronald K.

3b. SOCIAL SECURITY NUMBER

3c. POSITION TITLE
Associate Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
University of Southern California
School of Medicine
2025 Zonal Avenue
Los Angeles, CA 90033

3e. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
Preventive Medicine

3f. MAJOR SUBDIVISION
Medicine

3g. TELEPHONE *(Area code, number and extension)*
(213)224-6500

4. HUMAN SUBJECTS
☐ NO ☒ YES ☐ Exemption # _____ OR ☐ Form HHS 596 enclosed

5. RECOMBINANT DNA
☒ NO ☐ YES

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD
From: 7/1/86 Through: 6/30/91

7. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD *(from page 4)*
$ 296,376

8. DIRECT COSTS REQUESTED FOR ENTIRE PROPOSED PROJECT PERIOD *(from page 5)*
$ 1,279,807

9. PERFORMANCE SITES *(Organizations and addresses)*
Shanghai Cancer Institute
Department of Epidemiology
270 Dong-An Road
Shanghai, PRC

Dept. of Applied Biological Science
Massachusetts Institute of Technology
Cambridge, MA 02139

University of Southern California
School of Medicine
2025 Zonal Avenue, Los Angeles, CA 90033

10. INVENTIONS *(Competing continuation application only)*
☒ NO ☐ YES ☐ Previously reported OR ☐ Not previously reported

11. APPLICANT ORGANIZATION *(Name, address, and congressional district)*
University of Southern California
University Park
Los Angeles, CA 90089-1147

Congressional District #28

12. TYPE OF ORGANIZATION
☐ Public, Specify ☐ Federal ☐ State ☐ Local
☒ Private Nonprofit
☐ For Profit *(General)*
☐ For Profit *(Small Business)*

13. ENTITY IDENTIFICATION NUMBER
195-1642394A1

14. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT
Code 011 Description School of Medicine

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE *(Name, title, address and telephone number.)*
Wm. C. Hromadka, Exec. Dir.
Dept. of Contracts & Grants
University of Southern California
University Park
Los Angeles, CA 90089-1147 (213)224-7033

16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Name, title, address and telephone number)*
Cornelius J. Pings
Sr. Vice President for Academic Affair
University of Southern California
University Park
Los Angeles, CA 90089-1147 (213)224-7033

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense *(U.S. Code, Title 18, Section 1001)*.

SIGNATURE OF PERSON NAMED IN 3a *(In ink. "Per" signature not acceptable)*
Ronald K Ross

DATE
10/23/85

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense *(U.S. Code, Title 18, Section 1001)*.

SIGNATURE OF PERSON NAMED IN 16 *(In ink. "Per" signature not acceptable)*
Cornelius J. Pings

DATE
10/31/85

PHS 398 (Rev. 5/82)

2025794625

ABSTRACT OF RESEARCH PLAN

KEY PROFESSIONAL PERSONNEL ENGAGED ON PROJECT

NAME	POSITION TITLE	DEPARTMENT AND ORGANIZATION
Ross, R. K.	Associate Professor	Prev. Med., U.S.C.
Yu, M. C.	Associate Professor	Prev. Med., U.S.C.
Henderson, B. E.	Professor, Chairman	Prev. Med., U.S.C.
Gao Yu-Tang	Director, Professor	Shanghai Cancer Inst.
Tu Ji-Tao	Associate Professor, Epidemiol.	Shanghai First Med. Coll.
Wogan, Gerald	Professor	Nutrition & Food Science, Mass. Inst. Tech.
Groopman, John	Associate Professor	Toxicology, MIT

ABSTRACT OF RESEARCH PLAN: State the application's long-term objectives and specific aims, making reference to the health relatedness of th project, and describe concisely the methodology for achieving these goals. Avoid summaries of past accomplishments and the use of the first persor The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. DO NOT EXCEEI THE SPACE PROVIDED.

This document describes a proposal to conduct a cohort study of 18,000 men, ages 45-64, living in a geographically defined area of metropolitan Shanghai, People's Republic of China. The target population had been previously identified as part of a cohort study of ambient pollution and lung cancer. Over a 2½ year period, blood and urine samples and detailed dietary histories will be collected on each subject. Among the major goals of the study are to (1) determine the independent and interactive roles of hepatitis B virus and aflatoxin exposure in the etiology of hepatocellular carcinoma. Evidence of chronic hepatitis B virus infection will be determined by RIA for HBsAg and evidence of aflatoxin exposure will be determined by urine measurements of aflatoxin metabolites and by comparison of individual dietary histories with food surveys of aflatoxin contamination; (2) to determine the independent and interactive roles of intake of salt (as estimated by urinary sodium/creatinine ratios), intake of nitrate and N-nitroso compounds (measured by urinary assays), and vitamin C deficiency (determined by a serum absorbance spectophotometry assay and by the detailed dietary history) in the etiology of stomach cancer; (3) to determine the role of cigarette smoking, alcohol consumption, intake of N-nitroso compounds and beta carotene/vitamin A deficiency (measured by dietary survey and by a high performance liquid chromatography serum assay) in the etiology of esophageal cancer; (4) to determine the role of beta carotene/vitamin A deficiency and any interactive effect with cigarette smoking in the etiology of lung cancer.

Follow-up of the cohort will be accomplished through cancer registration by the population-based Shanghai Cancer Registry, routine ascertainment of death certificates, and annual recontact of all cohort members.

VERTEBRATE ANIMALS INVOLVED ☒NO ☐YES If "YES," identify by common names and underline primates.

2025794626

TABLE OF CONTENTS

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b. Type the name of the Principal Investigator/Program Director at the top of each printed page and each continuation page.

SECTION 3. Appendix *(Six sets)* *(No page numbering necessary for Appendix)*

Number of publications: 4 Number of manuscripts: 1

Other items *(list):*

A. Study Questionnaire
B. Sample pages from the Table of Chinese Food Composition
C. Informed Consent form
D. Follow-up questionnaire
E. Curriculum Vitae of Dr. Xu Li-Wei
F. Four reprints and a manuscript
G. Consortium arrangements between USC and MIT
H. Consortium arrangements between USC and Shanghai Cancer Institute

☒ Application Receipt Record, Form PHS 3830
☒ Form HHS 596 if Item 4, page 1, is checked "YES" and no exemptions are designated.

2025794627

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K.

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 7/1/86 THROUGH 6/30/87

DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only) NAME	POSITION TITLE	TIME/EFFORT %	Hours per Week	SALARY	FRINGE BENEFITS	TOTALS
Ross, Ronald	Principal Investigator			REDACTED		
Yu, Mimi C.	Co-P.I.			---	---	---
Henderson, Brian E.	Co-P.I.			---	---	---
To be named	Data processor		40			
Kazuko Arakawa	Programmer		20	REDACTED		
To be named - Visiting Chinese Scientist (40 hr/wk, 1/1/87-6/30/87)			40	REDACTED		
Fringe benefits - 24.6%				REDACTED		
		SUBTOTALS →				

CONSULTANT COSTS

C.S. Yang - $200/day x 8 + $80 per diem; $1759 round trip airfare + $15/diem ground transportation (see attached) — 4,118

EQUIPMENT *(Itemize)*

Revco, -70°C 17 cu ft 220 v/50HZ freezer, $5550 (including shipping)
Revco, -20°C 21 cu ft 220 v/50HZ freezer, $3300 (including shipping) x 9=$29700
24 tube table top centrifuge, $1200
Freezer alarms $75 x 10 = $750

29,700
5,550
750
1,200
37,200

37,200 ✓

SUPPLIES *(Itemize by category)*

Miscellaneous office supplies, $1,000
Computer supplies, $500
Needles, auto separator blood drawing tubes, urine collection containers
Blood storage tubes, urine storage tubes, labels (see attached)=7,000 @ $2/person=$14,000

15,500

TRAVEL	DOMESTIC	
	FOREIGN (see attached)	~~6,840~~
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

CONSORTIUM/CONTRACTUAL COSTS

Shanghai Cancer Institute (see attached) $103,160
Massachusetts Institute of Technology (see attached) $ ~~55,763~~ 55,487
Adjustment to MIT's IDC Rate

158,647
~~158,923~~

OTHER EXPENSES *(Itemize by category)*

Cable/telephone, $ 500
Computer time, $6,000

6,500

TOTAL DIRECT COSTS *(Also enter on page 1, item 7)* → ~~$296,100~~ $296,376

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. ACS

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)		REDACTED	~~81,898~~ 80,522 ✓	REDACTED	REDACTED	REDACTED
CONSULTANT COSTS		REDACTED	---	REDACTED	---	REDACTED
EQUIPMENT		37,200	30,225	---	---	---
SUPPLIES		15,500	10,450	1,815	1,997	2,196
TRAVEL	DOMESTIC					
	FOREIGN	6,840	~~7,524~~ 7,114	8,276	9,104	10,014
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
CONSORTIUM/ CONTRACTUAL COSTS		~~158,923~~ 158,647	~~136,576~~ 132,325	~~88,854~~ 88,246	~~95,995~~ 91,779	~~111,070~~ 95,447
OTHER EXPENSES		6,500	7,150	10,605	11,666	12,833
TOTAL DIRECT COSTS		~~296,376~~ 296,100	273,823	219,499	230,027	260,082

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Also enter on page 1, item 8)* → $1,279,807

JUSTIFICATION (Use continuation pages if necessary): Describe the specific functions of the personnel and consultants. If a recurring annual increase in personnel costs is anticipated, give the percentage. For *all* years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and consortium/contractual costs. For any additional years of support requested, justify any significant increases in any category over the first 12 month budget period. In addition, for COMPETING CONTINUATION applications, justify any significant increases over the current level of support. *Personnel will have to be recalculated in light of the new start date

Personnel has been increased 6% ~~and~~ other costs have been increased 10% per year.

Dr. Yu is currently the recipient of a Research Career Development Award. We have included (25%) of Dr. Yu's salary after expiration of that award on 6/30/88.

In years 2, 3, 4 and 5, the salary of the Visiting Chinese Scientist is for the entire 12 months.

We have increased computer expenses to $10,000 per year beginning in year 3.

The current negotiated fringe benefit rate is 24.6% per DHHS Rate Agreement dated January 14, 1985. This rate is used as the forecasted rate for University Fiscal Year (UFY) 87 (which begins July 1, 1986) and UFY 88.

✓ [illegible] [illegible]
[illegible]

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR OR AWARD CANDIDATE (Last, first, middle)	SOCIAL SECURITY NUMBER
ROSS, Ronald K.	

USC

BUDGET JUSTIFICATION

Personnel

Dr. Ross will devote 15% of his time as the principal investigator of this study.

Dr. Henderson is a co-principal investigator and will devote 2% of his time to this study.

Dr. Yu is a co-principal investigator who will supervise all aspects of data management and direct the analysis. She will devote 25% of her time to this project beginning in year 3 when analysis of data commences.

Data Processor: will be responsible for data entry and edit.

Kazuko Arakawa: will be responsible for the management of data and all respects of computer programming related to data processing and statistical analysis.

Visiting Chinese Scientist: We propose to bring one epidemiologist to the US annually to participate in the processing and analysis of data to facilitate intimate scientific interaction between US and Chinese investigators involved in this collaborative project.

Consultant

CS Yang, Ph.D. of the New Jersey School of Medicine will serve as a consultant in Years 1, 3, and 5 on this project. He will be responsible for advising on the laboratory arrangements and the analysis of blood samples for ascorbic acid, carotenes and retinol.

Equipment

We estimate that storage of 14000 (2 per person) 8cc urine samples, 7000 25cc urine samples, and 7000 2cc serum samples at -20°C will require about eight 21 cu ft freezers at the cost (including shipping) of $3300 per freezer. Because of the difficulty of getting adequate service and maintenance in Shanghai we have requested a ninth freezer for emergency use.

9 freezers x 3300/freezer = $29,700.

We will require an additional 1 x -70°C freezer for storing 7,000 x 2cc serum samples for the vitamin assays @ $5500 (including shipping).

We have requested 6 x -20°C freezers and 1 additional -70°C freezer for storing the 4000 samples we expect to collect in Year 2.

To minimize the chances that samples will thaw unexpectedly, we have requested freezer alarms for each of the 10 freezers in Year 1. ($75.00 per alarm x 10 = $750.) and for each of the 7 freezers in Year 2.

We will purchase a 24 tube table top centrifuge in Year 1 to assist in processing samples @ $1200 (including shipping).

In year 2, we plan to purchase and send to Shanghai the following additional laboratory equipment: (1) A minireader microtiter plate reader with digital read out for use in assaying blood specimens from liver cancer cases and controls for hepatitis B virus serologies ($3300 including shipping); (2) A Millapour Waters Co. 440 absorbance detector wave length kit with a 280-436 nm filter ($1050).

Supplies

We recently shipped the following supplies to Shanghai for collection of blood and urine samples for 7000 persons in 1985-86. The total costs for purchasing and delivering these supplies to Shanghai was $12,750. We have increased this by 10% to cover inflationary increases in 1986-87 (year 1). We plan to collect the same number of samples in the first funding year as in 1985-86 and about 4000 in year 2.

7000 x 21 G x 1" Blood Collecting Needles
14000 x 8cc Transpsort Mailing Tubes
7000 x 500cc Urine Collection Containers
7000 x 10ml Sterile Auto Separator Blood Tubes
14000 x 2ml Cryotubes with Screw Stopper
70000 Specimen Labels
7000 x 25cc Urine Storage Tubes.

Travel(Foreign)

Visiting Chinese Scientist: Round trip airfare from Shanghai to Los Angeles is $1600.

Drs. Ross and Yu plan to make one trip each to Shanghai annually to monitor the progress of the study. $1600 round trip airfare LA to Shanghai plus $85/day per diem x12 days x 2 trips = $5240.

Shanghai Subcontract PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. AC;

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD DIRECT COSTS ONLY

FROM 7/1/86 THROUGH 6/30/87

DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only) NAME	POSITION TITLE	TIME/EFFORT %	TIME/EFFORT Hours per Week	SALARY	FRINGE BENEFITS	TOTALS
Gao Yu-Tang	Principal Investigator					
Tu Ji-Tao	Co P.I.					
To be named	Field Personnel x9					
To be named	Data editor/coder x2					
To be named	Lab manager x 2					
To be named	Data manager					
*Fringe calculated at 100%	(see attached)					
	SUBTOTALS →			REDACTED	REDACTED	

REDACTED

CONSULTANT COSTS	Shanghai Sub Contract	
EQUIPMENT (Itemize) (see attached) 6000 watt back-up electrical generator		20,000
SUPPLIES (Itemize by category) Miscellaneous office supplies, $1500 Miscellaneous lab supplies, $1500		3,000 ✓
TRAVEL	DOMESTIC (see attached)	4,800 ✓
	FOREIGN	
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	
ALTERATIONS AND RENOVATIONS (Itemize by category)		
CONSORTIUM/CONTRACTUAL COSTS		
OTHER EXPENSES (Itemize by category) (see attached) Questionnaire reproduction costs (7000 x 28 pages @ .04¢/pg)=	7,840	
Questionnaire shipping costs to U.S. =	2,500	
Payment to participants (see attached) =	35,000	
Cable/telephone to U.S.	500	45,840 ✓
TOTAL DIRECT COSTS (Also enter on page 1, item 7) →		$103,160 ✓

2025794632

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. 43092 01 BA

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

China, Sub. to Shanghai Cancer Institute, Sub contract

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)		REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
CONSULTANT COSTS						
EQUIPMENT		20,000	---	6,365*	6,620	6,884
SUPPLIES		3,000	~~3,300~~ 3,120	~~6,930~~	~~7,293~~	~~7,791~~
TRAVEL	DOMESTIC	4,800	~~5,280~~ 4,992	~~5,808~~ 5,192	~~6,389~~ 5,399	~~7,028~~ 5,615
	FOREIGN					
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
CONSORTIUM/ CONTRACTUAL COSTS						
OTHER EXPENSES		45,840	29,049 SIBT	7,114 SIBT	~~7,826~~ 7,399 4%	~~8,609~~ 7,695 4%
TOTAL DIRECT COSTS		103,160	~~70,101~~ 67,862	~~48,200~~ 47,019	~~57,691~~ 48,900	~~57,730~~ 50,155

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD *(Also enter on page 1, item 8)* → $ 331,882

JUSTIFICATION (Use continuation pages if necessary): Describe the specific functions of the personnel and consultants. If a recurring annual increase in personnel costs is anticipated, give the percentage. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and consortium/contractual costs. For any additional years of support requested, justify any significant increases in any category over the first 12 month budget period. In addition, for COMPETING CONTINUATION applications, justify any significant increases over the current level of support.

All costs have been increased ~~10%~~ 4% annually.

We have calculated fringe benefit rates at 100% for years 1-5 of this proposal. This rate was previously negotiated between representatives of the US National Cancer Institute and the Shanghai Cancer Institute for an ongoing contract (RF# NO1-CP-210121, "Epidemiologic Studies of Cancer in China.")

* Grantee Calculated Supplies by Adding a 10% increase to the 02 year level for ongoing work and adding in the 04 year level to cover new procedures which would just start in the 03 year (See page 10 of NCI Home followed A Similar procedure using the 4% FACTOR instead of the 10% FACTOR

2025794633

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR OR AWARD CANDIDATE (Last, first, middle)	SOCIAL SECURITY NUMBER
ROSS, Ronald K.	

SHANGHAI

BUDGET JUSTIFICATION

Personnel

Dr. Gao will devote 10% of his time as the principal investigator of the Shanghai portion of this study.

Dr. Tu will devote 20% of his time as co-principal investigator and will be responsible for overseeing the day to day activities of the field personnel.

Field personnel x 9: We will hire retired nurses from the Shanghai Cancer Institute to contact study subjects, obtain consents, administer questionnaires, and collect and process blood and urine specimens. Each field worker will be responsible for collecting about 65 samples per month for 9 months or 585 anually. We plan to hire 12 persons for 9 months annually to collect 7020 samples (9 full-time equivalents at $960 each).

Years 3-5 will involve brief follow-up questionnaires and no sample collection; we have decreased the number of field personnel from 9 to 6 for these years.

Data Editor x 2: The data editors will be responsible for checking all questionnaires for completeness and for appropriate coding, for maintaining log books and for assuring that all samples and materials are appropriately labeled and stored. (2 x $960 each)

Lab Manager x 2: The lab managers will be responsible for processing and aliquoting all blood and urine samples. We will require only a single laboratory manager in years 3-5 and the budget has been adjusted accordingly. (2 x $1080 each)

Data Manager: The data manager will supervise the field personnel and the data editors.

In years 3, 4 and 5, we have requested salary support for a laboratory technician to perform the laboratory assays for this study. (annual salary $1106)

We have calculated fringe benefit rates at 100% for years 1-5 of this proposal. This rate was negotiated between representatives of the US National Cancer Institute and the Shanghai Cancer Institute for an ongoing contract (RF#N01-CP-21012) "Epidemiologic Studies of Cancer in China".

Equipment

Power outages are a common problem in Shanghai and no back-up system is currently available to supply the freezers being used in this study. We are requesting $20,000 to purchase a 6,000 watt back-up generator. The purchase will be made in Shanghai, so no shipping costs are involved.

Supplies

We have increased the Shanghai supply budget in years 3, 4 and 5 to cover costs of reagents and supplies for laboratory assays (HBsAg, serum carotenes/retinol, serum ascorbic acid, urinary Na/Cr, urinary nitrates and nitrosamines) to be conducted in China commencing in year 3 of this proposal.

DO NOT TYPE IN THIS SPACE—BINDING MARGIN

2025794634

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR OR AWARD CANDIDATE (Last, first, middle)	SOCIAL SECURITY NUMBER
ROSS, Ronald K.	

Travel (Domestic)

Since no public transportation will be readily available to transport nurses back to the Shanghai Cancer Institute at the completion of their daily schedule (between 9:00 and 9:30 p.m.), we have budgeted for daily taxi fare to provide this transportation. $20.00/day x 6 days/week x 40 weeks/year = $4,800.

Other Expenses

We estimate that the cost of reproducing 7000 x 28 page questionnaires and consent forms will be approximately $7840 (at $0.04/page) and that the cost of shipping these questionnaires to the US will be about $2500.

For medical research studies in Shanghai involving the collection of biologic samples such as blood and urine, payment to participants is required by law. We propose paying participants $5 US to satisfy this requirement and to enhance the participation rate. In Year 1, we expect 7000 participants and 4000 participants in Year 2.

DO NOT TYPE IN THIS SPACE—BINDING MARGIN

2025794635

MIT Subcontract

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. PH

DETAILED BUDGET FOR FIRST 12 MONTH BUDGET PERIOD
DIRECT COSTS ONLY

FROM 7/1/86 THROUGH 6/30/87

DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only) NAME	POSITION TITLE	TIME/EFFORT %	TIME/EFFORT Hours per Week	SALARY	FRINGE BENEFITS	TOTALS
Gerald N. Wogan	Principal Investigator			REDACTED		
To be named	Technical Asst					
SUBTOTALS →				REDACTED		

CONSULTANT COSTS — MIT Sub contract

EQUIPMENT (Itemize) — 0

SUPPLIES (Itemize by category)

C_{18} Sep-Paks (7000)	$17,500.
HPLC supplies (200 samples	1,500.
Antibody columns	750.
Chemicals	2,000.
	~~21,750~~

21,750

TRAVEL	DOMESTIC to collaborate with USC - 2 trips	1,200
	FOREIGN	
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	

ALTERATIONS AND RENOVATIONS (Itemize by category)

~~CONSORTIUM/CONTRACTUAL COSTS~~

Other Expenses:

Report and publication costs 250.

TOTAL DIRECT COSTS ---------- 34,464.

~~OTHER EXPENSES (Itemize by category)~~

Indirect Expenses ~~61.8%~~ MTDC 61.0 % per rate levels for December 1986 NIH ~~21,299~~ 21,023

TOTAL ~~DIRECT~~ COSTS (Also enter on page 1, item 7) → ~~55,763.~~ 55,478

PHS 398 (Rev. 5/82) PAGE 12

2025794636

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K.

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD (1 Ro1 CA 43092-01)
DIRECT COSTS ONLY

MIT Subcontract

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)		REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
CONSULTANT COSTS						
EQUIPMENT		0	25,000.	~~10,296~~ 4,500	0	0
SUPPLIES		21,750.	~~14,328~~ ~~9,900.~~ 10,181	~~10,494.~~	10,708 ~~11,124.~~	11,136 ~~11,791~~
TRAVEL	DOMESTIC	1,200.	1,248 ~~1,272.~~	1,298 ~~1,348.~~	1,350 ~~1,429.~~	1,404 ~~1,515.~~
	FOREIGN					
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
Other expenses		250.	~~1,750.~~ 1,760	~~1,855.~~ 1,830	~~1,966.~~ 1,904	~~2,084.~~ 1,980
Total Direct Costs		34,464.	~~49,862.~~ 49,693	~~26,353.~~ 25,607	~~27,935.~~ 26,632	~~29,611.~~ 27,697
Indirect expenses 61.8% 61%		~~21,299.~~ 21,023	~~15,613.~~ 15,020	~~16,813.~~ 15,620	~~18,102.~~ 16,246	~~19,484.~~ 16,895
TOTAL ~~XXXXXX~~ COSTS		~~55,763.~~ 55,487	~~65,475.~~ 64,643	~~43,166.~~ 41,327	~~46,037.~~ 42,878	~~49,095.~~ 44,592

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 8) → $ 259,536.

JUSTIFICATION (Use continuation pages if necessary): Describe the specific functions of the personnel and consultants. If a recurring annual increase in personnel costs is anticipated, give the percentage. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and consortium/contractual costs. For any additional years of support requested, justify any significant increases in any category over the first 12 month budget period. In addition, for COMPETING CONTINUATION applications, justify any significant increases over the current level of support.

All costs are increased by 6%/year.

Equipment - Year 2: High Pressure Liquid Chromatograph.

Supply costs are decreased in Year 2 to reflect a decrease in the number of Sep-paks purchased.

Other expenses: add 1500 for HPLC maintenance in 02 – 05 years.

Indirect expenses are estimated as:
Year 1 = 61.8% MTDC
Year 2 = 62.8% MTDC
Year 3 = 63.8% MTDC
Year 4 = 64.8% MTDC
Year 5 = 65.8% MTDC

2025794637

MIT

BUDGET JUSTIFICATION

Personnel

Technical Assistant: will spend the first two years refining the techniques of the assay for aflatoxin metabolites, which is still under development. This individual will analyse urine samples from study subjects starting in year 3.

Equipment

High Pressure Liquid Chromatograph - An HPLC is requested from this grant because the two HPLC's which are presently available in the laboratories, a Beckman Model 324 gradient liquid chromatograph and a Waters Model 204 gradient liquid chromatograph, are four years and 10 years old, respectively. By the end of the grant period they will be past the expected life-span of an instrument which is used on a daily basis. Both of these machines are currently being used 80% of the time and are committed to a number of different projects. We feel the request of a new instrument which will be used for the analysis of the aflatoxin samples and for the training of new personnel to run the analysis is reasonable.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. VA2

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Ross, Ronald K.	Associate Professor	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Rutgers University, New Jersey	B.A.	1971	Biological Science
University of Iowa	M.S.	1975	Prev Med Environ Hlt
University of Iowa	(M.D.)	1975	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Experience and Employment

1975-1976 Post Doctoral Fellow in Cancer Epidemiology, University of Iowa
1976-1979 Instructor, Department of Family & Preventive Medicine, University of Southern California
1979- Assistant Professor, Department of Family & Preventive Medicine, University of Southern California
1982- Associate Professor, Department of Family & Preventive Medicine, University of Southern California

Awards Career Development Award, 1980-1985

Publications (Selected from 61)

Ross RK, McCurtis JW, Henderson BE, Menck HM, Mack TM, Preston-Martin S. Descriptive epidemiology of testis and prostate cancer in Los Angeles. Brit J Cancer 39:284-292, 1979.

Casagrande JT, Pike MC, Ross RK, Louie EW, Roy S, Henderson BE. "Incessant Ovulation" and ovarian cancer. Lancet 2:170-174, 1979.

Ross RK, Hill AP, Gerkins VR, Pfeffer R, Arthur M, Henderson BE, Mack TM. A case-control study of menopausal estrogen therapy and breast cancer. J Amer Med Assoc 243:1635-1639, 1980.

Paganini-Hill A, Glazer E, Henderson BE, Ross RK. Cause-specific mortality among newspaper web pressmen. J Occup Med 22:542-544, 1980.

Ross RK, Deapen DM, Foster DB, Casagrande JT, Henderson BE. A cohort study of prostate cancer incidence in Catholic priests. Br J Cancer 43:233-235, 1981.

Yu MC, Ho JHC, Ross RK, Henderson BE. Nasopharyngeal carcinoma in Chinese -- salted fish or inhaled smoke? Prev Med 10:15-24, 1981.

Ross RK, Paganini-Hill A, Mack TM, Arthur M, Henderson BE. Menopausal estrogen therapy and protection from ischemic heart disease death. Lancet 1:858-859, 1981.

Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. A case-control study of menopausal estrogen therapy and hip fractures. Ann Int Med 95:28-31, 1981.

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Berg JW, Ross RK, Latourette HB. Economic status and survival of cancer. Cancer 39:967-977, 1977.

Gould-Martin K, Paganini-Hill A, Casagrande C, Mack TM, Ross RK. Behavioral and biological determinants of surgical stage of breast cancer. Prev Med 11:429-440, 1981.

Davidson BJ, Ross RK, Paganini-Hill A, Hammond GD, Siiteri PK, Judd HL. Total and free estrogens and androgens in postmenopausal women with hip fractures. J Clin Endor Metab 54:115-120, 1982.

Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. Cancer Res 42:3232-3239, 1982.

Paganini-Hill A, Ross RK. Reliability of recall of drug usage and other health related information. Am J Epidemiol 116:114-122, 1982.

Ross RK, Dworsky R, Nichols P, Paganini-Hill A, Kass M, Lukes RJ, Henderson BE. Gastrointestinal tract lymphomas and occupational exposure to asbestos. Lancet ii:1118-1120, 1982.

Weinberg DM, Ross RK, Mack TM, Paganini-Hill A, Henderson BE. Bladder cancer etiology, a different perspective. Cancer 51:675-680, 1983.

Laufer LR, Davidson BJ, Ross RK, et al. Physical characteristics and sex hormone levels in patients with osteoporotic hip fractures and endometrial cancer. Am J Obstet Gynecol 145:585-590, 1983.

Ross RK, Paganini-Hill A. Estrogen replacement therapy and coronary heart disease. Sem Reprod Endocrin 1:19-25, 1983.

Ross RK, Dworsky R, Mack TM, Paganini-Hill A, Boone J, Nichols P. The occurrence of multiple lymphoreticular and hematologic malignancies in the same households. Br J Cancer 47:853-856, 1983.

Gray GE, Paganini-Hill A, Ross R. Dietary intake and nutrient supplement use in a Southern California retirement community. Am J Clin Nutr 38:122-128, 1983.

Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? Prostate 4:333-344, 1983.

Henderson BE, Pike MC, Ross RK. Epidemiology and risk factors. In: Breast Disease: Recent Advances in Diagnosis and Treatment. G. Bonadonna (ed), Wiley, Chichester, pp 15-33, 1983.

Gray GE, Paganini-Hill A, Ross RK, Henderson BE. Assessment of three brief methods of estimation of Vitamin A and C intakes for a prospective study of cancer: comparison with dietary history. Am J Epidemiol 119:581-590, 1984.

Ross RK, Garbeff P, Paganini-Hill A, Henderson BE. The effect of in-utero exposure to DES on age at puberty and post-pubertal hormone levels in males. Can Med Assoc J 128:1197-1198, 1983.

Blanco D, Ross RK, Paganini-Hill A, Henderson BE. Cholecystectomy and colon cancer. Dis Colon Rectum 27:290-294, 1984.

Ross RK, Paganini-Hill A, Krailo M, Gerkins V, Henderson BE, Pike MC. Reserpine, prolactin and breast cancer. Cancer Res 44:3106-3108, 1984.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Brian E. Henderson	Professor & Chairman, Prev. Med.; Dir., Cancer Center	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
University of California, Berkeley	B.A.	1958	English
University of California, San Francisco		1960	
University of Chicago	M.D.	1962	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Research and Professional Experience:

1964-1969 Medical Officer, USPHS, Arbovirology Unit, CDC, Atlanta, GA
1969-1970 Chief, Arbovirology Unit, CDC, Atlanta, GA
1970-1974 Associate Professor of Pathology, University of Southern California School of Medicine
1974-1978 Professor of Pathology, University of Southern California School of Medicin
1974-1983 Associate Director, LAC/USC Cancer Center
1978- Professor and Chairman, Department of Preventive Medicine, University of Southern California School of Medicine
1983- Director, USC Comprehensive Cancer Center

Honors: Alpha Omega Alpha
Distinguished Scholar, National Academy of Sciences, 1980-1981

Advisory Committees:

1979-1981 NCI, Member, Board of Councillors DCCP
1979-1981 National Institutes of Medicine, Division of Health Promotion and Disease Prevention Advisory Council
1982- IARC Scientific Council
1982- General Motors Cancer Research Foundation/Mott Award Committee

Publications: (selected from more than 200)

Gray G, Williams P, Gerkins V, Armstrong B, Brown J, Casagrande J, Phillips R, Pike M, Henderson Diet and hormone levels in Seventh-Day Adventist teenage girls. Prev Med 11:103-107, 1982.

Gray G, Pike MC, Hirayama T, Tellez J, Gerkins V, Brown J, Casagrande J, Henderson BE. Diet a hormone profiles in teenage girls in four countries at different risk to breast cancer. Prev M 11:108-113, 1982.

Preston-Martin S, Henderson BE, Pike MC. Descriptive epidemiology of cancers of the upp respiratory tract in Los Angeles. Cancer 49:2201-2207, 1982.

Casagrande JT, Pike MC, Henderson BE. Re: "Menarcheal age and spontaneous abortion: A cau connection?" Amer J Epidemiol 115:481-483, 1982.

Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in hum cancer. Cancer Res 42:3232-3239, 1982.

Lam KC, Yu MC, Leung JWC, Henderson BE. Hepatitis B virus and cigarette smoking—Risk fact for hepatocellular carcinoma in Hong Kong. Cancer Res 42:5246-5248, 1982.

Preston-Martin S, Yu MC, Benton B, Henderson BE. N-nitroso compounds and childhood brain tumc Cancer Res 42:5240-5245, 1982.

Ross R, Dworsky R, Nichols P, Paganini-Hill A, Wright W, Koss M, Lukes R, Henderson B. Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. Lancet 2:1118-1120, 1982.

Armstrong RW, Armstrong MJ, Yu MC, Henderson BE. Inhalants and salted fish as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. Cancer Res 43:1967-1970, 1983.

Weinberg DM, Ross RK, Mack TM, Paganini-Hill A, Henderson BE. Bladder cancer etiology. A different perspective. Cancer 51:675-680, 1983.

Yu MC, Mack T, Hanisch R, Peters RL, Henderson BE, Pike MC. Hepatitis, alcohol consumption, cigarette smoking and hepatocellular carcinoma in Los Angeles. Cancer Res 43:6077-6079, 1983.

Preston-Martin S, Yu MC, Henderson BE, Roberts C. Risk factors for meningiomas in men in Los Angeles County. J Natl Cancer Inst 70:863-866, 1983.

Judd HL, Meldrum DR, Deftos LJ, Henderson BE. Estrogen replacement therapy: Indications and complictions. Ann Int Med 98:195-205, 1983.

Ottman R, Pike MC, King MC, Henderson BE. Estimating risk for familial breast cancer: A practical guide. Lancet 2:556-558, 1983.

Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in young women. Br J Cancer 47:749-756, 1983.

Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. Nature 303:767-770, 1983.

Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 2:926-930, 1983.

Henderson BE, Preston-Martin S, Edmondson HA, Peters RL, Pike MC. Hepatocellular carcinoma and oral contraceptives. Br J Cancer 48:437-440, 1983.

Henderson BE, Ross RK, Pike MC. Exogenous Hormones and the Risk of Cancer. In: Recent Advances in Cancer Control, Proceedings of the 6th Asia Pacific Cancer Conference (S Yamagata, T Hirayama, and S Hisamichi, Eds). Sendai, Japan, 1983, pp 73-85.

Preston-Martin S, Bernstein L, Maldonado AA, Henderson BE, White SC. A dental x-ray validation study: Comparison of information from patient interviews and dental charts. Amer J Epidemiology 121:430-439, 1985.

Henderson BE, Ross RK, Judd HL, Krailo MD, Pike MC: Regular ovulatory cycles increase breast cancer risk. Cancer (in press)

Wu AH, Henderson BE, Pike MC, Yu MC: Smoking and other risk factors for lung cancer in women. J Natl Cancer Inst 74:747-752, 1985.

Yu MC, Henderson BE, Ho JHC, Lai SH. Salted fish and nasopharyngeal carcinoma: report of a case-control study in Hong Kong. Cancer Res (in press)

Tannenbaum SR, Bishop W, Yu MC, Henderson BE. N-nitrosi compounds and mutagenicity in Chinese style salted fish. Natl Cancer Inst Monogr (in press).

Ross RK, Paganini-Hill A, Krailo MD, Gerkins VR, Henderson BE, Pike MC. Effects of reserpine on prolactin levels and incidence of breast cancer in postmenopausal women. Cancer Res 44:3106-3108, 1984.

Henderson BE, Paganini-Hill A, Ross RK. Protection from acute myocardial infarction among users of estrogen replacement therapy. JAMA (in press)

Yeh FS, Mo CC, Luo S, Henderson BE, Tong MJ, Yu MC. A serological case-control study of primary hepatocellular carcinoma in Guangxi, China. Ca Res 45:872-873, 1985.

Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J Natl Cancer Inst 74:741-745, 1985.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. YA9

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Mimi C. Yu	Associate Professor	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
University of Toronto, Canada	B.Sc.	1973	Mathematics
University of California, Los Angeles	M.S.	1974	Biostatistics
University of California, Los Angeles	Ph.D.	1977	Biostatistics

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Research and Professional Experience

1973-74 Research Assistant, Department of Psychiatry, UCLA School of Medicine
1974-75 Teaching Assistant, Biostatistics Division, UCLA School of Public Health
1974-75 Programmer, Health Sciences Computing Facility, UCLA Medical Center
1975-76 Teaching Associate, Biostatistics Division, UCLA School of Public Health
1976-77 Statistician, Department of Commuity Medicine, Charles R. Drew Postgraduate Medical School, Los Angeles
1977-78 Senior Statistician, Department of Community Medicine, Charles R. Drew Postgraduate Medical School, Los Angeles
1978-84 Assistant Professor of Research, Department of Preventive Medicine, University of Southern California School of Medicine
1984- Associate Professor of Research, Department of Preventive Medicine, University of Southern California School of Medicine

Honors
Arts and Science Alumni Prize, Toronto, 1973
Sister St. John Award, Toronto, 1973
Member, Delta Omega Society, 1974
UCLA Medical Center Auxiliary Award, 1974
Academic Scholar Award, 1977
NIH Research Career Development Award, 1983

Advisory Committees

1985- Member, Board of Scientific Counselors, Division of Cancer Etiology, National Cancer Institute

Publications (selected from 27)

Yu MC, Rubin RT. VARSLP: A computer program for the variable analysis of scored sleep data. Psychophysiology 13:273, 1976.

Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. Int J Cancer 23:598-602, 1979.

Wolde-Tsadik G, Yu MC. Concordance in variable-subset discriminant analysis. Biometrics 35:641-644, 1979.

Yu MC, Ho JH, Ross RK, Henderson BE. Nasopharyngeal carcinoma in Chinese - Salted fish or inhaled smoke. Prev Med 10:15-24, 1981.

Yu MC, Gerkins VR, Henderson BE, Brown JB, Pike MC. Elevated levels of prolactin in nulliparous women. Br J Cancer 43:826-831, 1981.

Peters JM, Preston-Martin S, Yu MC. Brain tumors in children and occupational exposure of parents. Science 213:235-237, 1981.

Yu MC, Dunn OJ. Robust tests for the equality of two correlation coefficients: a Monte Carlo study. Educational and Psychological Measurement 42:987-1004, 1982.

Lam KC, Yu MC, Leung JWC, Henderson BE. Hepatitis B virus and cigarette smoking: risk factors for hepatocellular carcinoma in Hong Kong. Cancer Res 42:5246-5248, 1982.

Preston-Martin S, Yu MC, Benton B, Henderson BE. N-nitroso compounds and childhood brain tumors: a case-control study. Cancer Res 42:5240-5245, 1982.

Preston-Martin S, Yu MC, Henderson BE, Roberts C. Risk factors for meningiomas in men in Los Angeles County. J Natl Cancer Inst 70:863-866, 1983.

Armstrong RW, Armstrong MJ, Yu MC, Henderson BE. Salted fish and inhalants as risk factors for nasopharyngeal carcinoma in Malaysian Chinese. Cancer Res 43:2967-2970, 1983.

Yu MC, Mack T, Hanisch R, Peters RL, Henderson BE. Hepatitis, alcohol consumption, cigarette smoking and hepatocellular carcinoma in Los Angeles. Cance Res 43:6077-6079, 1983.

Tong MJ, Yu MC, Co R, Eastin B. Hepatitis B virus markers in the foreign-born population of Chinese in Los Angeles, California. J Infect Dis 149:475, 1984.

Preston-Martin S, Henderson BE, Yu MC. Epidemiology of intracranial meningiomas: Los Angeles, California. Neuroepidemiology 2:164-178, 1984.

Mack TM, Peters JM, Yu MC, Hanisch R, Wright WE, Henderson BE. Pancreas cancer is unrelated to the workplace in Los Angeles. Am J Indust Med 7:253-266, 1985.

Yeh FS, Mo CC, Luo S, Henderson BE, Tong MJ, Yu MC. A serological case-control study of primary hepatocellular carcinoma in Guangxi, China. Cancer Res 45:872-873, 1985.

Wu A, Henderson BE, Pike MC, Yu MC. Smoking and other risk factors for lung cancer in women. J Natl Cancer Inst 74:747-751, 1985.

Yu MC, Ho JHC, Henderson BE, Armstrong RW. The epidemiology of nasopharyngeal carcinoma in Malaysia and Hong Kong. Natl Cancer Inst Monogr (in press).

Li CC, Yu MC, Henderson BE. Some epidemiological observations of nasopharyngeal carcinoma in Guangdong, China. Natl Cancer Inst Monogr (in press).

Wang QS, Yu MC, Henderson BE. Risk factors for breast cancer in Tianjin, China. Natl Cancer Inst Monogr (in press).

Tannenbaum SR, Bishop W, Yu MC, Henderson BE. N-nitroso compounds and mutagenicity in Chinese-style salted fish. Natl Cancer Inst Monogr (in press).

Yu MC, Ho JHC, Lai SH, Henderson BE. Cantonese-style stalted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. Cancer Res (in press).

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Gao Yu-Tang (Y.T. Gao)	Associate Professor of Medical Statistics and Epidemiology	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Harbin Medical College, Harbin, China		1954	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1956-63 Assistant, Department of Public Health and Medical Statistics, Postgraduate College of Public Health, Beijing.

1964-77 Vice-head, Department of Medical Statistics, Suchow Medical College, Suchow, Jiangsu Province.

1978- Associate Professor, Chief of the Department of Epidemiology, Shanghai Cancer Institute, Shanghai.

1979-80 Corrvissiano Fellow, Unit of Cancer Epidemiology and Biostatistics, Internatidnal Agency for Research on Cancer, Lyon, France.

1982-84 Vice-chairman of the Society of Epidemiology, Shanghai Medical Association.

1984- Member of the Society of Oncology, Shanghai Medical Association.

1985- Director, Shanghai Cancer Institute, Shanghai.

Publications

Statistical methods used in environmental monitoring. Publishing House of Atomic Energy, Beijing, 1980.

Incidence of childhood leukaemia in Shanghai. Int J Cancer 25:701-703, 1980.

Cancer mortality in Shanghai during the period 1963-77. Brit J Cancer 43:183-195, 1981.

A preliminary report of etiological and epidemiological studies on primary liver cancer in Chongming County of Shanghai. Shanghai Tumor 1(4):4-7, 1981.

The survival rate of 29682 cancer cases among workers of Shanghai Industry-Communication-Finance-Trade System. Shanghai Tumor 1(5):5-10, 1981.

Analysis of cancer incidence, mortality and survival rates in Shanghai urban area during 1972-79. Shanghai Tumor 2(3):1-7, 1982.

Cancer incidence in Shanghai during 1973-77. JNCI Monograph 62:43-46, 1982.

Cancer incidence and mortality of genitourinary system among males in Shanghai. Chinese J Urological Surgery 3(1):77-80, 1982.

Cancer incidence data in Shanghai. In "Cancer Incidence in Five Continents" Vol. IV. (Ed. Waterhouse J. et al) IARC Scientific Publications No. 42, 382-385, Lyon, France, 1982.

Handbook on cancer registration. National Office on Cancer Control Research, 1982.

The analysis of geographic clustering of cancer mortality rates in Shanghai. Shanghai Tumor 3:193-196, 1985

Incidence and mortality of female breast cancer in Shanghai during 1963-1980. Shanghai Tumor 4:110-112, 1985

Measurement of serum thiocynate -- a biochemical marker of smoking. Shanghai Tumor 5:169-170, 1985.

Prevalence of smoking among 110,000 adult persons in Shanghai urban area. Chinese J Preventive Medicine (in press).

Association of lung squamous cell carcinoma and adenocarcinoma with smoking. Shanghai Tumor (in press).

A population-based case-control study of lung cancer in Shanghai. JNCI Monograph (in press).

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. PI

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
TU Ji-Tao	Associate Professor Cancer Epidemiology	Dec. 16, 1928

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Dongji Medical University, PRC		1952	Medicine
Shanghai First Medical University, Shanghai, PRC		1953	Public Health

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Professional Experiencesz

Assistant Professor, Department of Epidemiology, Shanghai First Medical University, Shanghai, PRC 1953-1958
Lecturer, Department of Infectious Disease and Epidemiology, Chongking Medical College, Chongking, PRC 1958-1978
Lecturer, Department of Epidemiology, Shanghai Cancer Institute, Shanghai, PRC 1979-1980
Visiting Scholar, National Cancer Institute, Bethesda, USA 1981-1982
Associate Professor, Department of Epidemiology, Shanghai Cancer Institute, Shanghai, PRC 1981-date

REDACTED

Professional Service:

Editorial Board (member), Shanghai Journal of Tumor.
Editorial Board (member), Guangzhou Journal of Cancer.

Publications (selected from 41 papers):

1. F P Li, J T Tu, F S Liu, E L Shiang. Rarity of Ewing's Sarcoma in China. Lancet I:1255, 1980.
2. F P Li, F Jin, J T Tu, Y T Gao. Incidence of Childhood Leukemia in Shanghai. Int J Cancer 25:701, 1980.
3. Y T Gao, J T Tu, F Jin, R N Gao. Cancer Mortality in Shanghai during the Period 1963-77. Br J Cancer 43:183, 1981.
4. J T Tu, F P Li. Incidence of Childhood Tumors in Shanghai, 1973-77. JNCI 70:589, 1983.
5. R N Gao, J T Tu, Y T Gao. Research in Risk Factors for Primary Liver Cancer in Chongming County --- A Priliminary Report. Shanghai J Tumor 1:4, 1981.
6. B C Gu, R N Gao, J T Tu et al. HBV carrier rates among General Populations Living in Areas with Different Liver Cancer Rates. Chinese J Epid 4:37, 1983.
7. H C Chen, J T Tu. Suggestions on Cancer Control in Shanghai. Shanghai J Tumor 5:90, 1985.

(next page)

8. H King, J Y Li, F B Locke, E S Pollack, J T Tu. Patterns of Site-Specific Displacement in Cancer Mortality among Migrants: The Chinese in the United States. AJPH 75:237, 1985.
9. Q Y Young, J T Tu, H M Li et al. Risk Factors for Gastric Cancer in Deep Faulty Areas --- 1. The Assqciation of Drinking Water Types and Gastric Cancer. (submitted to Shanghai J Tumor, June, 1985)
10. J T Tu, R N Gao, D H Zhang et al. The Risk Factors of Primary Liver Cancer in the High Prevalence Area, Chongming County --- Results from A Five Years Follow-up. (presented at the German-Chinese Symposium on Cancer, June, 1985)
11. C N He, J T Tu, C Q Bao et al. Evaluation on Cancer Planned Control System in Yangpu District, Shanghai. (submitted to Shanghai J Tumor, Aug, 1985)

Program Director: ROSS, Ronald K.

BIOGRAPHICAL SKETCH

Give the following information for all professional personnel contributing to the training program, beginning with the Program Director. Photocopy this page for each person. Do not exceed two pages on any individual.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Gerald N. Wogan	Professor of Toxicology and Head, Department of Nutrition & Food Science	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Juniata College, Huntingdon, PA	B.S.	1951	Biology, Chemistry
University of Illinois, Urbana, IL	M.S.	1953	Physiology; Bioche
University of Illinois, Urbana, IL	Ph.D.	1957	Physiology; Bioche and Microbiology

RESEARCH AND TRAINING SUPPORT (See instructions)

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, exp ence, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO N EXCEED TWO PAGES.

1957-61 Assistant Professor of Physiology; Rutgers University
1961-62 Research Associate in Food Toxicology; MIT
1962-65 Assistant Professor of Food Toxicology; MIT
1965-69 Associate Professor of Food Toxicology; MIT
1969- Professor of Toxicology, MIT
1978- Director, Center for Health Effects of Fossil Fuels Utilization, MIT
1979- Underwood-Prescott Professor and Head, Department of Nutrition and and Food Science

1977 Elected to the National Academy of Sciences, USA

1975-82 Environmental Health Advisory Committee, US Environmental Protection Agency
Chairman, Study Group on Guidelines for Mutagenicity Testing
Chairman, Study Group on Pesticide Tolerances
1976-82 National Cancer Advisory Board
Chairman, Subcommittee on Environmental Carcinogenesis 1979-82
1975-79 Toxicology Study Section; National Institutes of Health
Chairman, 1976-79
1977-82; Board on Toxicology and Environmental Health Hazards; National Academy
1984- of Sciences/National Research Council
Chairman; 1984-

Publications:

Croy, R.G., J.E. Nixon, R.O. Sinnhuber, and G.N. Wogan. Investigation of covalent aflatoxin B_1-DNA adducts formed in vivo in rainbow trout (Salmo gairdneri) embryos and liver. Carcinogenesis 1(11): 903-909, 1980.

Croy, R.G. and G.N. Wogan. Temporal patterns of covalent DNA adducts in rat liver after single and multiple doses of aflatoxin B_1. Cancer Res. 41: 197-203, 1981.

Bennett, R., J.M. Essigmann, and G.N. Wogan. Excretion of an aflatoxin-guanine adduct in urine of aflatoxin B_1-treated rats. Cancer Res. 41: 650-654, 1981.

Croy, R.G. and G.N. Wogan. Quantitative comparison of covalent aflatoxin-DNA adducts formed in rat and mouse livers and kidneys. J. Natl. Cancer Inst. 66(4): 761-768, 1981.

Huagen, A., J.D. Groopman, I.-C. Hsu, G.R. Coodrich, G.N. Wogan and C.C. Harris. Monoclonal antibody to aflatoxin B_1-modified DNA detected by enzyme immunoassay. Proc. Natl. Acad. Sci. USA 78(7): 4124-4127, 1981.

Groopman, J.D., R.G. Croy, and G.N. Wogan. In vitro reactions of aflatoxin B_1-adduc DNA. Proc. Natl. Acad. Sci. USA 78(9): 5445-5449, 1981.

Loosemore, M.J., G.N. Wogan and C. Walsh. Determination of partition ratios for allylisopropylacetamide during suicidal processing by a phenobarbital-induced cytochr P-450 isozyme for rat liver. J. Biol. Chem. 256(16): 8705-8712, 1981.

Groopman, J.D., K.W. Fowler, W.F. Busby, Jr., and G.N. Wogan. Interaction of aflat B_1 with rat liver DNA and histones in vivo. Carcinogenesis 2(12): 1371-1372, 1981.

Busby, W.F., Jr. and G.N. Wogan. IN: Mycotoxins and N-Nitroso Compounds: Envir mental Risks, Volume II, R.C. Shank, ed., CRC Press, Boca Raton, FL, Chapters 1 through 12, pp. 1-193, 1981.

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Imamura, T., W.F. Busby, Jr., M.E. Goldman, G.N. Wogan and H. Brunengraber. Eff of hydroxyurea and benzo(a)pyrene on DNA synthesis in the isolated perfused rat lun Bull. Environ. Contam. Toxicol. 28 (2): 135-140, 1982.

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Donahue, P.R., J.M. Essigmann, and G.N. Wogan. IN: Indicators of Genotoxic Exposu Banbury Report 13. Aflatoxin-DNA adducts: Detection in urine as a dosimeter of exposure. B.A. Bridges, B.E. Butterworth, I.B. Weinstein, eds. Cold Spring Harbor Laboratory, pp. 221-229, 1982.

Essigmann, J.M., R.G. Croy, R.A. Bennett and G.N. Wogan. Metabolic epoxidation of aflatoxin B_1 and its metabolites: Patterns of DNA adduct formation and removal in relation to biological effects. IN: Chemical Carcinogenesis. C. Nicholini, ed., Plenum Press, NY. pp. 47-66, 1982.

Nordheim, A., W.M. Hao, G.N. Wogan and A. Rich. Salt-induced conversion of B-DNA to Z-DNA inhibited by aflatoxin B_1. Science 219(4591): 1434-1436, 1983.

Irvin, T.R. and G.N. Wogan. Quantitation of AFB_1 adduction within the ribosomal RNA gene sequences of rat liver DNA. Proc. Natl. Acad. Sci. USA 81(3): 664-668, 1984.

Croy, R.G., J.M. Essigmann, and G.N. Wogan, Aflatoxin B_1: Correlations of patterns of metabolism and DNA modification with biological effects. IN: Organ and Species Specificity in Chemical Carcinogens. R. Langenbach, S. Nesnow, and J.M. Rice, eds. Plenum Press, New York, NY, pp. 49-62, 1983.

Busby, W.F., Jr., and G.N.Wogan. Tumorigenicity of fluoranthene in a newborn mouse lung adenoma bioassay. Carcinogenesis, In Press.

Groopman, J.D., Trudel, L.J., Donahue, P.R., Marshak-Rothstein, A. and G.N. Wogar High affinity monoclonal antibodies for aflatoxins and their application to solid phase immunoassays. Proc. Natl. Acad. Sci. USA, 81: 7728-7731, 1984.

Busby, W.F., Jr., Shuker, D.E.G., Charnley, G., Newberne, P.M., Tannenbaum, S.R and G.N. Wogan. Carcinogenicity of the nitrosated bile acid conjugates, N-nitrosoglycocholic acid and N-nitrosotaurocholic acid. Cancer Res. In press.

Wogan. G.N., Chemical and biochemical dosimetry of exposure to genotoxic chemicals. In: The Role of Chemicals and Radiation in the Etiology of Cancer. Raven Press, In Press.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

BIOGRAPHICAL SKETCH

PBA

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
John D. Groopman, Ph.D.	Associate Professor of Toxicology	REDACTED

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Elmira College, Elmira NY	B.A.	1974	Chemistry
Massachusetts Institute of Technology, Cambridge MA	Ph.D.	1979	Toxicology
Massachusetts Institute of Technology, Cambridge MA		1979-1980	Postdoctoral Fellow

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE

1974-1979: NIEHS Predoctoral Fellow, Laboratory of Toxicology, Massachusetts Institute of Technology, Gerald N. Wogan, Ph.D., Advisor

1979-1980: NIEHS Postdoctoral Fellow, Laboratory of Toxicology, Massachusetts Institute of Technology, Gerald N. Wogan, Ph.D., Advisor

1980-1981: Staff Fellow, Laboratory of Human Carcinogenesis, National Cancer Institute, National Institutes of Health, Curtis C. Harris, M.D., Advisor

1980-Present: Research Affiliate, Laboratory of Toxicology, Massachusetts Institute of Technology

1983-1984: Assistant Professor of Microbiology, Boston University School of Medicine

1981-1984: Assistant Professor of Toxicology and Environmental Health, Boston University School of Medicine, School of Public Health

1984-Present: Associate Professor of Toxicology and Microbiology, Boston University School of Medicine/School of Public Health

HONORS

American Association for Cancer Research
Phi Beta Kappa

PUBLICATIONS

1. Wogan, G.N., Croy, R.G., Essigmann, J.M., Groopman, J.D., Thilly, W.G., Skopek, T.R. and Liber, H.L. Mechanisms of Action of Aflatoxin B_1 and Sterigmatocystin: Relationships of Macromolecular Binding to Carcinogenicity and Mutagenicity. In Environmental Analysis, P. Emmelot and E. Kriek, eds., Elsevier/North Holland Press, Amsterdam, 1979, pp.97-121.

2. Groopman, J.D., Busby, W.F. and Wogan, G.N. Distribution and Time Course of Aflatoxin B_1 Binding to Rat Liver Nuclei and Identification of Histone H_1 as a Major Site of AFB_1 Adduction to Rat Liver Chromosomal Proteins in vivo. Proc. Amer. Assoc. Cancer Res. 20:182, 1979.

3. Groopman, J.D., Busby, W.F. and Wogan, G.N. The Nuclear Distribution of Aflatoxin B_1 and Its Interaction with Histones in vivo. Cancer Res. 40:4343-4351, 1980.

4. Wogan, G.N., Essigmann, J.M., Croy, R.G., Busby, W.F., Groopman, J.D. and Stark, A.A Macromolecular Binding of Aflatoxin B_1 and Sterigmatocystin: Relationships of Adduct Patterns to Carcinogenesis and Mutagenesis. In Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis. E.C. Miller, et al., eds. University Park Press, Baltimore, 1980, pp.19-33.

5. Groopman, J.D., Busby, W.F., Fowler, K.W. and Wogan, G.N. A comparison of Aflatoxin B_2 to Aflatoxin B_1 Binding with Rat Liver DNA and Histones in vivo. Proc. Amer. Assoc. Cancer Res. 21:71, 1980.

6. Groopman, J.D., Croy, R.G. and Wogan, G.N. In vitro Reactions of Aflatoxin B_1 Adducted DNA. Proc. Natl. Acad. Sci. USA 78:5445-5449, 1981.

7. Haugen, A., Groopman, J.D., Hsu, I.C., Goodrich, G.R., Wogan, G.N. and Harris, C.C. Monoclonal Antibody to Aflatoxin B_1 Modified DNA Detected by Enzyme Immunoassay. Proc. Natl. Acad. Sci. USA 78:4124-4127, 1981.

8. Groopman, J.D., Fowler, K.W. Busby, W.F., Jr., and Wogan, G.N. Interaction of Aflatoxin B_1 with Rat Liver DNA and Histones in vivo. Carcinogenesis 2:1371-1373, 1981

9. Groopman, J.D., Haugen, A., Goodrich, G.R., Wogan, G.N. and Harris, C.C. Quantitation of Aflatoxin B_1 Modified DNA Using Monoclonal Antibodies. Cancer Res. 42:3120-3124, 1982.

10. Groopman, J.D., Kohn, K.W., Strong, J. and Erickson, L. Preparative HPLC Analysis of the Interaction of Chloroethylnitrosoureas with the DNA of L1210 Cells in Culture. Proc. Amer. Assoc. Cancer Res. 24:210, 1983.

11. Kensler, T.W., Enger, P.A., Trush, M.A., Mello, C.J. and Groopman, J.D. Modification of Aflatoxin B_1 Binding to DNA by Antioxidants. Proc. Amer. Assoc. Cancer Res. 25:129, 1984.

12. Groopman, J.D., Trudel, L.J., Marshak-Rothstein, A. and Wogan, G.N. High Affinity Monoclonal Antibodies Recognizing Aflatoxins and Aflatoxin-DNA Adducts. Proc. Amer. Assoc. Cancer Res. 25:98, 1984.

13. Skipper, P.L., Bryant, M.S., Tannenbaum, S.R. and Groopman, J.D. Analytical Methods for Assessing Exposure to 4-Aminobiphenyl Based on Protein Adduct Formation. In Medical Screening and Biological Monitoring for the Effects of Exposure in the Workplace. In press, 1984.

14. Groopman, J.D., Trudel, L.J., Donahue, P.R., Marshak-Rothstein, A. and Wogan, G.N. High Affinity Monoclonal Antibodies for Aflatoxins and Their Application to Solid Phase Immunoassays. In press, Proc. Natl. Acad. Sci. USA, 1984.

15. Groopman, J.D., Mello, C.J. and Mandel, R. Human Placental Mediated Mutagenesis and DNA Adduct Formation in vitro by Aflatoxin B_1. Submitted to Cancer Letters.

16. Groopman, J.D., Strong, J., Erickson, L.C., Kohn, K. Identification of DNA Adducts Produced in L1210 Cells by Chloroethylnitrosoureas. In preparation for Carcinogenesis

17. Weiss, A., Moolten, F. and Groopman, J.D. Interactions of Aflatoxin B_1 with DNA of FAO Rueber Cells in Culture. In preparation.

18. Groopman, J.D. Chemical Activation of Aflatoxins to Protein Binding Species. In preparation.

19. Kensler, T.W., Enger, P.A., Trush, M.A., Mello, C.J. and Groopman, J.D. Modification of Aflatoxin B_1 Binding in vivo to Rat DNA by Dietary Antioxidants. Carcinogenesis 6, in press, 1985.

20. Wolff, T., Distlerath, L.M., Worthington, M., Groopman, J.D., Kadlubar, F.F., Prough, R.A., Martin, M.V., and Guengerich, F.P. Substrate Specificity of Human Liver Cytochrome P-450 Debrisoquine 4-Hydroxylase Probed Using Immunochemical Inhibition and Chemical Modeling. Cancer Research, 45:in press, 1985.

21. Roberts, D., Benson, R., Flammang, T., Kadlubar, F., Groopman, J., Nagel, W., and Moss, G. Characterization of Antisera to DNA Adducts of the Human Bladder Carcinogen 4-Aminobiphenyl. Submitted to Fed. Proc.

OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K., M.D.

(1) ACTIVE SUPPORT:

NCI/CA32197/The role of estrogens and vitamin A in disease prevention/ A.P-Hill. $127,070/4-1-82 thru 3-31-87.

NCI/CA36388/Case-control study of multiple myeloma/R.K. Ross/ $78,948/ 5-1-85 thru 4-30-90.

NCI/CA36301/Serial immune and viral studies in men with "pre-lymphoma"/ A. Levine/ no salary/$130,852/8-1-84 thru 7-31-87.

NCI/CP51025/Analgesic use and cancer of the renal pelvis/R.K. Ross, $71,397/12-85 thru 8-87.

NCI/CA17054/Program Project Grant USC Cancer Center Epidemiology and Biostatistics Unit/B.E. Henderson/ $1,379,363/1-1-75 thru 3-31-87.

(3) PLANNED:

None

*Current Award

2025794653

OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposa pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, no Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifyi number, project title, name of principal investigator/program director, time or percent of effort on the project by profession named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent proje and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overla duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of th scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: R.K. Ross, M.D.

(1) ACTIVE SUPPORT:

NCI/CA32197/The Role of Estrogens and Vitamin A in Disease Prevention/ B.E. Henderson, $127,070/4-1-82 - 3-31-87.

NCI/CA36388/Case-Control Study of Multiple Myeloma/R.K. Ross/ $78,948/5-1-85 - 4/31/90.

NCI/CA17054/USC Cancer Center Epidemiology and Biostatistics Unit/ B.E. Henderson/ /$1,370,281/1-1-75 - 3-31-87.

2) Pending:

None

3) Planned:

None

OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

[redacted] Co-P.I.: Brian E. Henderson, M.D.

(1) ACTIVE SUPPORT:

NCI/CA14089/Cancer Center Core Support Grant/B.E. Henderson, $1,951,362/12-1-84 through 11-30-89.

NCI/CA32197/The Role of Estrogens and Vitamin A in Disease Prevention/ B.E. Henderson/ $127,070 (no salary)/4-1-82 through 3-31-87.

NCI/R01-CA40468/Salted Fish and Nasopharyngeal Carcinoma/B.E. Henderson/ (no salary)/$227,495/10-1-85 through 9-30-88.

NCI/CA17054/USC Cancer Center Epidemiology and Biostatistics Unit/B.E. Henderson/ $1,370,281/1-1-75 through 3/31/87.

(2) PENDING:

None

(3) PENDING:

None

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OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying *number, project title, name of principal investigator/program director, time or percent of effort on the project by professional* named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

~~PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR~~ Co-P.I.: Mimi C. Yu, Ph.D.

(1) ACTIVE SUPPORT:

NCI/Career Development: Environmental Factors in Cancer Etiology/M. Yu/ (salary support $40,000)/7-1-83 through 6-30-88.

(2) PENDING:

None

(3) PLANNED:

None

2025794656

ROSS, Ronald K.

GERALD N. WOGAN

RESEARCH SUPPORT

ACTIVE

National Institutes of Health P01-ES00597	Study of Food-Borne Environmental Toxicants Co-Principal Investigator	Grant Period Subproject Total for Current Year Total Percent Effort *NS	4/1/76 - 3/31/86 $579,787 TDC
National Institutes of Health P01-ES01640	Effects of Modification of Macromolecules in vivo and in vitro Byproducts of Fossil Fuels Combustion [Project D-2] Co-Principal Investigator	Grant Period Current Year Percent Effort *NS	7/1/83 - 6/30/86 $ 56,823 TDC
National Institutes of Health P30-ES02109	Environmental Health Sciences Ctr. (Administration and Core Unit C) Co-Principal Investigator	Grant Period Current Year Percent Effort *NS	4/1/84 - 3/31/89 $ 48,285 TDC
National Institutes of Health T32-ES07020	Training Program in Environmental Toxicology Program Director	Grant Period Current Year Total Costs *NS	7/1/85 - 6/30/90 $327,034
American Cancer Society SIG-10			
Department of the Army DAMD17-85-C-5208	Mycotoxin Studies-Segment 1	Grant Period Current Year Percent Effort	7/31/85 - 7/31/86 $ 57,764

*On all of these, Wogan receiv no salary.

GERALD N. WOGAN

RESEARCH SUPPORT (continued)

PENDING

PLANNED

None.

Revised 8/16/85

Approved by:_____

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. YB11

OTHER SUPPORT

(Use continuation pages if necessary)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications and proposals pending review or funding; (3) applications and proposals planned or being prepared for submission. Include *all* Federal, non-Federal, and institutional grant and contract support. If none, state "none." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professions named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent project and the subproject and give the annual direct costs for each.) Describe the contents of each item listed. If any of these overlap duplicate, or are being replaced or supplemented by the present application, delineate and justify the nature and extent of the scientific and budgetary overlaps or boundaries.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

(1) ACTIVE SUPPORT:

JOHN D. GROOPMAN

2025794659

RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proxin and extent of availability to the project. Use "other" to describe the facilities at any other performance sites listed in Item 9, page 1, and at sites field studies. Using continuation pages if necessary, include an explanation of any consortium arrangements with other organizations.

☐ Laboratory:

☐ Clinical:

☐ Animal:

☒ Computer: Computer analyses will be done on the VAX computer of the USC Comprehensive Cancer Center, located in the Norris Cancer Research Hospital and Institute. The computer operates under the VMS System (Version 3.6), has 4 megabytes of memory, 2RP07 fixed drives (512 megabytes each), 2 tape drives, 2 line printers and card reader. A library of prewritten analysis routines, as well as the SAS statistical package are available and maintained by the staff of the Cancer Center's Biostatistics Laboratory (described below).

☒ Office: The University and the Norris Cancer Center provide offices for use by the project personnel at USC.

☐ Other (_____):

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities each.

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project.

This study will be conducted within the framework of the Cancer Epidemiology Program at the USC Comprehensive Cancer Center. The Cancer Center Epidemiology Program was formed in 1970 and has developed under the direction of Brian E. Henderson, M.D., Professor and Chairman, Department of Preventive Medicine, and Director of the LAC/USC Comprehensive Cancer Center. The program is part of the Department of Preventive Medicine of the University of Southern California School of Medicine, and since 1974 has been an integral part of the USC Cancer Center. This unit includes three major components: The Cancer Surveillance Program, a population-based

tumor registry of Los Angeles County under the direction of Thomas Mack, M.D.; 2) the Biostatistics Resource Laboratory, developed under the direction and leadership of Malcolm Pike, Ph.D. from 1973-1983, and currently under the direction of Duncan C. Thomas, Ph.D.; 3) the Epidemiology Field Studies Program under the direction of Dr. Henderson.

DO NOT TYPE IN THIS SPACE—BINDING MARGIN

2025794661

RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe the facilities at any other performance sites listed in Item 9, page 1, and at sites for field studies. Using continuation pages if necessary, include an explanation of any consortium arrangements with other organizations.

[X] Laboratory: The hybridoma lab, located in Building 26, room 033, is approximately 425 sq ft. dedicated to the development, production and testing of monoclonal antibodies. Hybridomas are produced through the fusion of spleen cells from an immunized mouse and mouse myeloma cells (Sp-2). From this union hybridomas are selected and grown for their specific monoclonal antibody production. Testing is carried out by two methods; RIA using an LKB liquid scintillation counter, and micro ELISA read with a single wavelength photometer measuring light absorbance.

[ ] Clinical:

[ ] Animal: The laborator is equipped with four laminar flow hoods and two incubators. Its working capacity is approximately four to six people, incubator space the limiting factor. There are available two microscopes; one inverted phase for tissue culture and a dissecting scope for clone work.

[ ] Computer:

[ ] Office:

[ ] Other ( ):

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Auxillary equipment include three centrifuges, liquid nitrogen cell storage system, cold box, freezer and water purification apparatus.

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such as consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project.

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FACILITIES: Mark the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proximi and extent of availability to the project. Use "other" to describe the facilities at any other performance sites listed in Item 9, page 1, and at sites f field studies. Using continuation pages if necessary, include an explanation of any consortium arrangements with other organizations.

[X] Laboratory: one for serum immunology assay; one for chemical assay; one for biochemical assay; four for storing serum and urine samples.

[ ] Clinical:

[ ] Animal:

[X] Computer: IBM-PCXT with hard disk and typing.

[ ] Office:

[ ] Other (_____):

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities o each.

PHLC

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such a consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project.

2025794963

INTRODUCTION

The People's Republic of China (PRC) offers special opportunities for conducting epidemiologic research aimed at understanding causes of cancer. Among the already well documented advantages are the opportunity to investigate the etiology of cancers which are less common in the United States, to test hypotheses not readily testable in this country, high participation rates and the relatively low cost.

This document describes a proposal for a large cohort study in Shanghai, PRC. Among the hypotheses we hope to investigate are (1) the interaction, if any, between aflatoxin and hepatitis B virus (HBV) in the etiology of hepatocellular carcinoma (HCC); (2) the independent and interactive roles of dietary sodium intake (as estimated by urinary sodium/creatinine ratios), intake of N-nitroso compounds (as estimated by urinary nitrosamines), and vitamin C deficiency in the etiology of stomach cancer; (3) the association between dietary vitamin A and beta (B-) carotene and development of epithelial, especially lung, cancers; and (4) the independent and interactive roles of cigarette smoking, alcohol consumption, intake of N-nitroso compounds, and various nutritional deficiencies in the etiology of esophageal cancer.

Not only is each of these relationships important to understand for biological reasons, but also because each has important implications for prevention, either through vaccination, dietary intervention, better food storage, or smoking and alcohol cessation and prevention programs.

Through private funds, we have begun the data collection phase of this study and expect to accumulate blood and urine samples, and diet questionnaires, on 7000 men (out of a total proposed sample size of 18,000) by the summer of 1986. We have no funds to continue the data collection after that date, or for the necessary follow-up period and laboratory work.

Because of the complexity of this proposal, we found it necessary to exceed slightly the page limitation on background information.

A. SPECIFIC AIMS

1) To determine through a cohort study of 18,000 middle-aged men the independent and interactive roles of HBV and aflatoxin exposure in the etiology of HCC in a high risk area of the PRC. Evidence of chronic infection will be determined by radioimmunoassay for hepatitis B surface antigen (HBsAg). Evidence of aflatoxin exposure will be determined by urine measurements of aflatoxin metabolites, and by comparison of individual dietary histories with food surveys of aflatoxin contamination.

2) To determine the independent and interactive roles of salt intake, vitamin C deficiency and intake of N-nitroso compounds in the etiology of stomach cancer in a high risk area of PRC. Salt intake will be estimated by urinary sodium/creatinine ratios. Serum vitamin C levels will be measured by absorbance spectophotometry and will be compared to dietary intake of vitamin C measured by individual dietary histories. Intake of N-nitroso compounds and nitrates will be estimated by urinary assays.

3) To determine the role of B-carotene and vitamin A deficiency in the etiology of multiple epithelial cancers in PRC, especially cancer of the lung, and to determine any interaction between smoking and B-carotene or vitamin A deficiency in the etiology of lung and esophageal cancer. Serum B-carotene and retinol will be determined by high performance liquid chromatography and these levels will be compared to dietary intakes measured by individual dietary surveys.

4) To determine the independent and interactive roles of cigarette smoking, alcohol consumption, B-carotene or vitamin A deficiency, and intake of N-nitroso compounds in the etiology of esophageal cancer in a high risk population of PRC.

B. BACKGROUND AND SIGNIFICANCE

Liver Cancer

An estimated 250,000 new cases of HCC occur each year worldwide with almost one-half of these occurring in China (1). HCC ranks third in cancer deaths in China behind cancer of the stomach and lung.(2) There is remarkable geographic variation of HCC in China with particularly high mortality rates in provinces along the southeast coast and in the three provinces of northeastern China.(2) Mortality rates are highest in the Provinces of Fujian and Jiangsu and in the Autonomous Region of Guangxi and lowest in the inland mountainous provinces. There is considerable evidence that chronic HBV infection is the major cause of HCC in China and probably worldwide:

Beasley et al have observed a significant correlation between the prevalence of HBsAg carriers by province of origin among adult males living in Taiwan and the province-specific liver cancer mortality rates.(3)

Several case-control studies of the association between HCC and HBV in China have been reported.(4-10) Early reports were based on insensitive serological assays and probably underreported the true frequency of HBsAg+ individuals in both cases and controls.(4-8) We recently reported results from two case-control studies among Chinese in Hong Kong and Guangxi Autonomous Region, respectively, in which hepatitis B markers were measured by radioimmunoassay.(9-10) These studies indicate a strong association between chronic HBV infection and risk of HCC in these Chinese populations (see preliminary studies for details, page 47).

The largest cohort study of HBV and HCC to date was initiated in Taiwan in 1975 among male Chinese government employees.(11) Between 1976 and 1978, nearly 23,000 men were administered a questionnaire and a blood specimen was obtained. After 140,000 man-years of follow-up (mean of 6.2 years per man), 116 men had developed HCC. Among the 3,454 men who were initially HBsAg+, 113 developed HCC compared to only 3 among the 19,253 who were initially HBsAg-. The age-adjusted relative risk was 271. We are involved in a second prospective study in Chongming Island near Shanghai (12) (see preliminary studies for details, page 47).

Before the strong association between HBV and HCC was established, aflatoxins in food-stuffs were thought to be the most probable cause of HCC. Although aflatoxins are established hepatic carcinogens in many animal species (13,14), the role of aflatoxins in the genesis of HCC in China, and in other parts of Asia and Africa where exposure to aflatoxins is common, remains uncertain. Several studies have demonstrated that aflatoxin contamination of human foods is correlated on an international basis with incidence of HCC.(15-17) In Guangxi Autonomous Region of PRC, average levels of consumption of foods that had previously been shown to be frequently contaminated with aflatoxins (peanuts, peanut oil, corn and beans) were calculated for

individual villages.(18) The villages were then grouped into "light" and "heavy" consumption areas. The mortality rate of HCC among HBsAg+ individuals in the heavy consumption villages was 10 times higher than among HBsAg+ individuals in the light consumption villages. These rates, however, were based on small numbers. We have conducted several studies to help determine further what role, if any, aflatoxins play in the etiology of HCC in China (see preliminary studies for details, page 47).

As noted at a recent World Health Organization meeting, "unique opportunities" exist, for the first time, "to prevent a common human cancer by HBsAg immunization".(19) It is likely that some 90% of HCC in China is causally related to HBV infection. Inactivated 22nm HBsAg particle vaccines have been licensed for use and field tests have so far indicated that the vaccine is safe and effective. The major remaining issue is the most appropriate vaccine schedule for the protection of the majority of individuals, since in China about 50% of infants born to HBsAg+ mothers are chronic carriers by 12 months of age.(20) Even after an acceptable vaccine program has been launched, cases of liver cancer will continue to occur for many decades in those previously infected early in life. Therefore it is important to determine what role, if any, aflatoxin exposure plays in aggravating the risk of HCC in HBV infected individuals. Immediate protection from exposure to aflatoxins may be a useful intermediate goal in HCC prevention.

A problem in previous studies of aflatoxin and HCC has been the failure to measure aflatoxin exposure on an individual basis. We propose a study in which we can determine the independent or interactive role of HBV and aflatoxin in the etiology of HCC in Shanghai. HBV exposure will be measured by radioimmunoassay of serum for HBsAg, and aflatoxin exposure by measurement of aflatoxin metabolites in urine and by a comparison of individual dietary histories with food surveys of aflatoxin contamination.

Stomach Cancer

Stomach cancer is among the most common cancers in Shanghai with an age-adjusted incidence rate of $56/10^5$.(21) Among environmental factors, smoking and various dietary factors have received the most attention as possibly playing an etiologic role. Although several large cohort studies in the US (22,23) and Japan (24) have found an association between smoking and stomach cancer, the failure to observe a clear dose-response relationship in each of these has raised doubts about the causality of this association. The role of smoking in the etiology of stomach cancer in China is unexplored.

Among dietary hypotheses, an association between stomach cancer and salty foods, and nitrates and related compounds, have received the most attention. Several case-control studies have reported an association between intake of certain salty foods and risk of stomach cancer (25,26), but assessing total salt intake by means of a dietary history has proven extremely difficult, since salt is often mixed with dietary items in unknown proportions. Sodium excretion in the urine is a good measure of sodium intake but precise measures of urinary sodium excretion require accurate 24-hour sample collections, which are impractical to obtain in large scale epidemiologic studies. Since individuals excrete creatinine at a nearly constant rate, use of the sodium/creatinine ratio has been suggested as an index of the rate at which the kidneys excrete sodium and, therefore, of dietary sodium intake. Correa et al have shown that populations living in geographic areas of Colombia with high risk to stomach cancer have sodium/creatinine ratios 35% higher than populations living in low risk areas.(27) These differences were not explained by age, sex, height or weight. Importantly, these results are identical to those based on direct measurement of sodium excretion in 24-hour urine samples. We recently compared urinary sodium/creatinine ratios in 3 populations at differing risk of stomach cancer (28) (see preliminary studies for details, page 48).

Assessing dietary intake of nitrates and related compounds presents similar methodologic problems to those described above for measuring salt intake. Nitrates are found in a variety of foods, including certain vegetables and cured meats.(29) These can be converted to nitrites by oral bacteria and nitrites, in turn, can combine with secondary amines from certain foods or medications under appropriate pH conditions in the stomach, to form nitrosamines. Nitrosamines are potent carcinogens in experimental settings. Vitamin C can prevent the formation of nitrosamines in vivo.(30,31) Several case-control studies have found a positive association between intake of cured meats (25,26) and a negative association between intake of fruits and stomach cancer risk.(26,32,33) A strong correlation between use of nitrate fertilizer and mortality from gastric cancer in 17 provinces of Chile has been reported (34) and a high death rate from gastric cancer in England has been correlated with high concentrations of nitrate in public water supplies.(35) While there are strong suggestive data, epidemiologic studies of stomach cancer are needed, which provide more precise measures of exposure to N-nitroso compounds and vitamin C intake.

Lung Cancer and Vitamin A

Several lines of evidence suggest that vitamin A (retinol) may be an effective anticancer agent.(36) Vitamin A and its analogues can prevent or delay the development of tumors in animals treated with carcinogens.(37,38) Laboratory evidence also suggests that vitamin A can reversibly suppress the malignant behavior of cultured cells transformed by external carcinogens.(39) The mechanism for this effect is thought to be related to the role played by vitamin A in the maintenance and growth of epithelial cells. Vitamin A deficiency, on the other hand, leads to cell dedifferentiation and squamous metaplasia.(40) The principal vitamin A precursor, B-carotene, because of its antioxidant properties, may itself be an anticancer agent.(36)

A series of case-control studies performed in a variety of settings and looking at a variety of cancer sites have consistently demonstrated that persons with low intake of B-carotene or vitamin A, or of foods rich in B-carotene or vitamin A, have a higher risk of cancer than persons with high intakes. The largest number of studies and the most consistent results relate to lung cancer (41-45), but similar results have been observed for stomach cancer (41), esophageal cancer (46), as well as for a variety of other sites.(47,48) In the only study to date of vitamin A supplements and cancer risk, men who used vitamin A supplements had a significantly lower risk of lung cancer than men who did not (RR=0.55), but no similar association was observed in women.(49)

Prospective studies of serum B-carotene and retinol levels and cancer risk have provided inconsistent results. Wald and colleagues collected blood samples on 16,000 men ages 35 to 64 years, who attended a health screening clinic in Oxford, England in 1975-1978.(50) Serum retinol levels of the 86 men who developed cancer by the end of 1979 were compared to those of 172 control men of similar age and smoking habits. The men who developed cancer had significantly lower retinol levels than men who did not and risk of cancer decreased with increasing quintiles of circulating retinol. The difference in mean retinol levels in lung cancer cases and controls was greater than for any other site.

Using samples collected from the Evans County, Georgia Cardiovascular Project, Kark et al reported that serum retinol levels were lower in persons who developed cancer than in healthy controls and that this relationship was present both for smokers and non-smokers.(51) A subsequent report from the same study was unable to confirm these results.(52) However, similar to the results of Wald et al, retinol levels in lung cancer cases in this second report were 13% lower than in controls, the largest site-specific difference observed.

A recent study of participants in the Hypertension Detection and Follow-up Program was reported by Willett et al.(53) Serum retinol and carotenoid levels of 111 subjects who were free of cancer at the

time of sampling but diagnosed as having cancer during the subsequent five years were compared with those of 210 cancer free controls matched for age, sex, race and time of blood collection. Mean retinol and carotenoid levels were similar. In fact, the 17 subjects with lung cancer actually had a slightly higher mean retinol level than their matched controls.

Nomura et al studied the relationship between B-carotene and vitamin A and cancer in a cohort study of 6800 Japanese men in Hawaii.(54) Vitamin A levels were unrelated to cancer development at any site but there was a significant association between serum B-carotene and lung cancer. The lung cancer odds ratio for men in the lowest quintile was 3.4 relative to men in the highest quintile.

Finally, in a follow-up study in Basel, Switzerland of cardiovascular and peripheral arterial disease, 38 men who died of lung cancer had significantly lower B-carotene levels than healthy controls but no difference was observed for serum retinol levels.(55)

Although results of serum studies have been inconsistent, the most promising results to date relate to lung cancer. No serum studies have been reported in populations likely to have relatively low dietary intake of B-carotene or vitamin A and little is known about the interaction of retinol/B-carotene and cigarette smoking in modifying lung cancer risk.

Esophageal Cancer

Cancer of the esophagus is the 4th most common cancer in men in Shanghai.(21) The age-adjusted mortality rate in men is 23 per 100,000, some 5 times the rate of whites in the US. Vitamin A deficiency has been thought to play a role in the pathogenesis of esophageal cancer in other high risk areas of China (56).

Heavy consumption of alcohol and tobacco are well established risk factors for esophageal cancer in North America and Western Europe, and it appears that 90% of risk in these areas can be attributed to exposure to these factors either individually or jointly.(57) The joint effect of these two factors appears to be multiplicative and very high relative risks have been observed for these two factors in combination in some studies. For example, in a case-control study of males in Brittany conducted by Tuyns et al in 1977, the relative risk for men in the highest category of smoking (> 1 1/2 packs per day) and ethanol consumption (>120 gms. per day) was 156 compared to persons who neither smoked or drank.(58) However, there is evidence that in some of the highest risk areas of the world, alcohol and smoking may be less important factors. In Northern Iran, one of these areas, alcohol is not a risk factor and cigarettes play only a minor role. (46,59) The role of alcohol and smoking in the etiology of esophageal cancer in China has not been well studied, although for Chinese in Singapore these factors also appear to be relatively unimportant (60). Any interaction between vitamin A deficiency and smoking and alcohol consumption in the etiology of esophageal cancer is unstudied.

Other dietary factors may be important in the pathogenesis of esophageal cancer in China. In the highest risk area of China, Lin-xian County in Hunan Province, a high content of N-nitrosamine precursors-nitrate, nitrite, and secondary amines-as well as preformed nitrosamines has been found in various foods, including pickled vegetables (61,62), a food item frequently eaten by inhabitants and related to mortality from esophageal cancer.(63) Saliva samples collected from subjects with epithelial dysplasia or carcinoma in this region have higher levels of nitrate and nitrite than those collected from healthy subjects. Lu et al recently collected 24 hour urine samples from healthy subjects of Lin-xian and Fan-xian, a low risk esophageal cancer area in northern China.(64) The levels of four urinary N-nitrosoamino acids and nitrate were measured. The amounts of N-nitrosoproline, N-nitrosothiazolidine,4-carboxylic acid, N-nitrososarcosine, and nitrate were all signficantly higher in the urines from Lin-xian. Vitamin C can prevent the formation of nitrosamines in vivo. Intake of moderate doses of ascorbic acid by subjects in this high risk area substantially reduced urinary levels of N-nitrosoamino acids.(63) A consistent finding among case-control studies of specific food items and esophageal cancer conducted outside China has been a history of low intake of fresh fruits and vegetables in esophageal cancer patients compared to controls. (41,46,65)

C. PRELIMINARY STUDIES

Liver Cancer

We studied the role of HBV and aflatoxin exposure in the etiology of HCC in a case-control study among Chinese in Hong Kong (9). HBsAg was measured by radioimmunoassay using kits supplied by Abbott Laboratories. We attempted to quantitate consumption of foods most likely to be contaminated by aflatoxin. Eighty-eight (82%) of the HCC cases in this study were HBsAg+ compared to 19 (18%) controls (relative risk (RR)=21.3, 95% confidence interval (CI)=10.1, 45.9). There was little difference between HCC cases and controls in consumption of foods likely to be contaminated with aflatoxins. Another interesting finding in this study was the strong association between HCC and cigarette smoking among persons who were HBsAg-. This association was most apparent in the older age group. The RR for heavy smokers in this group was 8.2 compared to non-smokers (95% CI=1.5, 91.9).

We were involved in another case-control study of HCC which was recently completed in the Guangxi Autonomous Region of PRC.(10) In that study, 43 cases (86%) were HBsAg+ compared to 11 controls (22%), yielding a RR estimate of 17.0 (95% CI=4.3, 99.4). Six of the 7 HBsAg- cases were positive for both anti-HBs and anti-HBc.

We have conducted a cohort study of HBV and aflatoxin exposure, and HCC risk on Chongming Island near Shanghai.(12) A total of 12,222 men over 40 years of age were interviewed and a blood sample collected. At 3 years of follow-up there had been 70 HCC deaths. The age-adjusted mortality rate of HCC in HBsAg+ individuals according to the less sensitive reverse passive hemagglutination assay was $651/10^5$ compared to $99/10^5$ among HBsAg- individuals (RR=6.7). The use of the less sensitive assay may explain the lower relative risk observed in this study compared to previous studies. In this study individual consumption of a variety of foods was assessed at the outset. On this island maize is known to be the most widely used food item with a high likelihood of aflatoxin contamination. There was an increasing risk of HCC among HBsAg+ individuals with increasing consumption of maize, whereas no definite pattern was seen in HBsAg- individuals:

Table 1
Adjusted Mortality Rate of HCC by Level of Maize Consumption

Maize as % of all staple foods	HBV Carrier			Non-Carrier		
	Total Person-years	No. Deaths	Rate	Total Person-Year	No. Deaths	Rate
Non-eater	589.5	2	272.9	2314.5	2	99.8
-24%	4230.5	27	640.8	20691.5	21	104.8
25-50%	341.0	4	1333.4	2392.0	0	0.0
50+%	99.5	1	1117.4	456.0	0	0.0

Stomach Cancer

We previously collected overnight (12 hr) urine specimens in a study of diet and hormone profiles in teenage girls at different risks of developing breast cancer.(28) Using a Beckman Astra, we measured urinary sodium and potassium in samples from girls in the US, Chile and Japan by ion selective electrode methods and creatinine by the kinetic alkaline picrate method. Results, together with age-adjusted female stomach cancer mortality rates, are shown below. The sodium/creatinine ratio for US teenage girls is significantly lower than those of teenage girls from Chile and Japan (analysis of variance, pairwise $p<0.001$, Scheffe method). There were only small statistically non-significant differences in the potassium/creatinine ratio. Adjustment for age, height and weight did not alter the findings.

Table 2

Mean values of sodium, potassium, creatinine and the sodium/creatinine and potassium/creatinine ratios in overnight (12h) urine samples of teenage girls from the United States, Chile and Japan.

	US	Chile	Japan
Number of samples	48	39	43
Sodium (mEq/l)	141.1	145.1	207.8
Potassium (mEq/l)	42.2	40.5	43.0
Sodium/creatinine*	1.14	1.82	1.99
Potassium/creatinine	0.34	0.45	0.40
Female stomach cancer mortality rate**	3.13	20.12	25.41

*US differs significantly from Chile, Japan (pairwise $p<0.001$, Scheffe Test)

**Age-adjusted rate per 100,000 female population, 1978

Lung Cancer

The Shanghai Cancer Institute is participating in a case-control study of lung cancer with the US National Cancer Institute (Contract NO1-CP-21012l). A total of 1200 incident lung cancer cases and an equal number of randomly selected controls have been interviewed. Participation rates for cases and controls exceed 90%.

Pilot Study

In order to determine the compliance rate and the feasibility of establishing a blood and urine bank and conducting a large longterm cohort study in Shanghai, we conducted a pilot study in March and April, 1985.

In 1983, the Shanghai Cancer Institute initiated a study to evaluate the role of general air pollution relative to cigarette smoking in the pathogenesis of lung cancer in Shanghai. Three geographically defined populations within the greater Shanghai municipality were defined. These regions were chosen because they were comparable in size and in certain demographic characteristics to one another (sex, age, and educational levels), because they were fairly typical of the entire municipality of Shanghai in terms of these demographic characteristics, and because the three areas represented high, moderate and low average annual levels of ambient pollution, respectively. The highly polluted area was geographically in the heart of the urban area, the moderate pollution area was in the suburban area, and the low pollution area was a more rural region. In 1983, a cross-sectional survey was conducted of these 3 areas and brief interviews were conducted with male residents ages 40-69, concerning cigarette smoking habits, occupation and residential history. Participation rates averaged 93%. An identification card was completed on each participant, with name, sex, address, and date of birth. About 27,000 men participated in the urban area, 25,000 in the suburban area, and 28,000 in the rural area.

The urban area of this study consists of 4 "streets", the administrative units of metropolitan Shanghai. For our pilot study we selected a random sample of 688 participants, ages 45-64, from one of these streets. We developed a brief questionnaire to confirm smoking habits, occupational history and certain demographic characteristics, and to obtain ahistory of alcohol use, a dietary history, and a brief medical history. A (10 cc) blood sample, a 50 cc midstream urine sample and a completed interview were obtained on 530 subjects (76%). Fifty-two subjects (8%) refused participation, another 8% were unavailable to participate either because they had moved (2%), had returned to the rural part of Shanghai upon retirement (5%) or had died (1%). Another 8% of patients were excluded either because they were acutely ill (3%) or were on temporary travel (5%). We expect that most of the latter two groups will be picked up in the main study described below.

Blood samples from the pilot study were centrifuged and the serum divided into 3 equal aliquots and stored at -20oC. Two X 8cc urine samples have also been stored at -20oC. An additional 25ml of urine was centrifuged and stored in a C18 Sep-pak cartridge (see below under laboratory methods, page 57). All serum samples have been tested in Shanghai for HBsAg by radioimmunoassay using reagents provided by Abbott laboratory. The positivity rate was 22%. Dr. Xu Li-Wei (see CV attached, Appendix E) from the Shanghai Cancer Institute will hand carry these serum samples and Sep-paks to the US on or about November

15,1985. He will spend two weeks in Los Angeles working in the laboratory of Dr. Myron Tong, Director of Liver Center, Huntington Memorial Hospital. The samples will be retested for HBsAg in order to determine the reliability of this assay, as performed by the laboratory of the Shanghai Cancer Institute. Dr. Xu will then travel to Newark, New Jersey to work with Dr. C.S. Yang, a consultant on this study, to test these pilot blood samples for retinol and carotene, using a high performance liquid chromatography assay developed by Dr. Yang (56) (see laboratory methods for details, page 55). We hope to have results on the range and mean of circulating levels of each of these micronutrients in middle-aged men in Shanghai prior to the review of this proposal. The Sep-pak cartridges will then be carried by Dr. Xu to Dr. Gerald Wogan's laboratory at MIT for measurement of aflatoxin metabolites (see laboratory methods for details, page 57).

D. METHODS

Identification of Target Population

In 1983, the Shanghai Cancer Institute began a large cohort study to evaluate the role of general air pollution relative to cigarette smoking in the pathogenesis of lung cancer in the Shanghai municipality. Three geographically defined areas in the greater Shanghai area were identified. These three regions were of comparable size and were similar to each other in terms of sex and age distribution and mean educational level, and also were representative of the entire Shanghai urban area on these three demographic factors. The three populations were located in the Shanghai urban area, suburban area and rural area, respectively, and represented areas of high, intermediate and low general air pollution. These three areas each contained between 25,000 and 30,000 middle-aged men (ages 40-69) about 92%-94% of whom are now participants in the air pollution and lung cancer cohort study. Each of these 3 areas consists of 4 "streets" which are the administrative units of Shanghai. Each street has a police station which keeps complete rosters of all residents and these rosters were used to identify the target population in each area. Each person identified who qualified by age and sex was invited to participate by providing information on cigarette smoking, occupational history and residential history. An identification card was completed on each participant with name, sex, date of birth and address and these were filed alphabetically by street. For the cohort study described in this proposal we have chosen to focus on the 27,000 participants in the urban area of this larger cohort study. Since the Shanghai population is more difficult to follow after retirement (see section on follow-up, page 54), we have placed an upper age limit on our target population of 64. Since most of the cancers under study in this proposal are strongly age-related, we have also eliminated the under 45 age group, the group with the lowest expected cancer rates.

Data Collection

Beginning on November 1, 1985 we will begin to recontact all men ages 45-64 who are currently participants in the urban portion of the Shanghai air pollution study. We plan to hire retired nurses from the Shanghai Cancer Institute to conduct the field work for this study. The interviewers will be trained on administering the attached questionnaire (see Appendix A). The questionnaire includes personal information (name, sex, address, education, occupation, plans for residence upon retirement), detailed cigarette smoking habits and alcohol use habits, a brief medical history, and a comprehensive food frequency history. Questionnaires will be administered using a questionnaire script, including all introductory and transitional statements to be read as written. Basic instructions, when required, precede each group of questions. In the development of the questionnaire, compound subjects, negatives, "loaded" words, contingency questions and imprecise definitions have been avoided.

There is no method of assessing past diet that is universally accepted as valid and reliable. The commonly used methods - dietary history, food record, 24 hour recall and food frequency - are all suspect with respect to validity and reliability. Fortunately in this study, for most of the dietary issues the dietary questionnaire data can be supplemented with more reliable laboratory data (retinol, carotenes, ascorbic acid, aflatoxin, salt, nitrates and nitrosamines).

To assess dietary habits in the proposed study we will use a comprehensive food frequency questionnaire which assesses usual consumption of a wide variety of foodstuffs commonly consumed in Shanghai. The dietary questionnaire was modeled after the diet questionnaire being used in the collaborative lung cancer case-control study between the US National Cancer Institute and the Shanghai Cancer Institute. Seasonal consumption is taken into account. Using this information and nutrient tables regarding specific Chinese foods provided to us by the Chinese Academy of Medical Sciences in Beijing (see examples attached, Appendix B), we will be able to estimate total intake of certain nutrients including vitamin C and carotenes. The US National Cancer Institute is expanding the Chinese food composition tables to include vitamin A. We will also be able to estimate intake of fat and dietary fiber and, using information available to the Shanghai Cancer Institute on aflatoxin contamination of different foodstuffs in Shanghai, compare the degree of aflatoxin exposure. We have previously performed such comparisons in the Chongming island cohort study (12) and in a case-control study in Hong Kong.(9)

Each interviewer will be expected to complete interviews with 3-4 subjects per working day. A weekly roster with preassigned numbering for each study subject will be assigned to each nurse. Nurses will contact the patients in their homes and reasons for non-participation will be carefully recorded. Since many of the participants in this study will be employed during the day, we expect that most of the field work will be completed between 4:30 and 9:30 P.M. Based on our pilot study we expect that the participation rate at first contact will be about 76%. We expect that about 8% of potential participants will refuse, and another 8% will now be unavailable due to death or change of residence. We expect that an additional 8% will be unable or unwilling to participate at first contact due to an acute illness or other reasons, but will probably agree to participate at a later date. We expect the final participation rate to approach 85%. Reasons for non-response will be carefully recorded.

When a person agrees to participate, he will be read and asked to sign the attached consent form (see Appendix C) and the questionnaire will then be administered. Responses that do not fit any coding category will be recorded verbatim. A label bearing the preassigned study number will be attached to the questionnaire.

At the completion of the interview the nurse will collect a 10cc blood sample using a vacuutainer and an auto-separator blood tube. The tube will be labeled with the preassigned and preprinted study number and placed on an ice pack in a styrofoam container. The

interviewee will be asked to provide a urine specimen in the 500cc prelabeled container provided. Each evening at the completion of her daily workload, the nurses will return to the Institute, centrifuge and store 1X2cc serum sample at -70°C and 1 X2cc serum sample at -20°C and refrigerate the urine specimens for processing the next morning.

Blood samples will be centrifuged in the auto separator tubes and the serum drawn off and aliquoted into 2X2cc plastic storage tubes. Each tube will be labeled with the study subject's unique identifying number. One tube will be stored at -70oC and the second at -20oC.

Urine samples will be aliquoted into 2X8cc and 1X25cc storage tubes, prelabeled with each study subject's identifying number, and stored at -20oC. Twenty-five ml of the remainder of the sample will be centrifuged for 10 minutes and the supernatant transferred to a 50ml beaker. 200ul of a tritiated chromatographic standard in 50% ethanol and 1.25 ml of methanol will then be added to the urine so that the final concentration is 5% methanol. The urine sample will then be loaded into a syringe and pushed through the C18 Sep-pak cartridge at a flow rate of 2-3 ml per minute. A 10ml solution of 5% methanol/95% water will then be loaded into the syringe and pushed through the Sep-pak at a comparable flow rate. The Sep-Pak will then be placed back into its foil packet, sealed with tape to prevent drying, and stored at 4oC.

Data Management

Questionnaires will be checked for completeness initially by the nurse interviewers. The questionnaire will then be rechecked by a data manager for internal consistency and to code any sections which have not been precoded. Any special situations regarding coding will be noted in writing in a code book. If necessary, respondents will be recontacted by the interviewer to clarify responses or resolve inconsistencies.

The data manager will be responsible for confirming that all urine samples and blood samples have been processed and stored and the study subject will be entered in the master log book with the locations of the stored urine and blood samples.

We plan to invite one Chinese epidemiologist annually to Los Angeles beginning in January, 1987. The Chinese scientist will participate in all aspects of data processing. During the first two years, data management will primarily involve entry and edit of questionnaire data which will be mailed to Los Angeles on a regular basis. Beginning in year 3 when biologic specimens of study subjects will be tested (see time schedule of laboratory testing for details, page 58) and the cohort followed (see follow-up for details, page 54) on a regular basis, the emphasis of data processing will be on entry and edit of laboratory values and update of study subjects' morbidity and mortality status. The Chinese scientist will also participate in data analysis during the later years of this study.

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Follow-up

The cohort will be followed for cancer occurrence in a variety of ways.

(1) Death Certification

The Shanghai municipality is divided into 12 urban districts (each containing a number of "streets"). Each of these districts has its own Vital Statistics Unit. Copies of death certificates for men who were residents of the streets being covered by our cohort study will be routinely ascertained and matched against our alpha file. Death certificates contain name and address, date of death and cause of death, and, if death occurred in a hospital, the name of the hospital. We will attempt to confirm causes of death due to cancer for any cancers not previously reported to our cancer registry (see below).

This will be accomplished by sending an employee to the hospital for record of deaths which occur in a hospital setting. For deaths occurring outside of a hospital, we will send an employee to the deceased individual's residence to attempt to learn more about the circumstances of death, and to ascertain whether there was any contact with the health care system prior to death, through which we might be able to document the primary cancer site.

For persons who maintain a Shanghai address upon return to rural areas at retirement (a fairly common occurrence, but for which we have no accurate statistics), death notification is received by the appropriate Vital Statistics Unit in Shanghai. Death notification is rapid since relatives must receive written permission from the Office of Public Security before burial can occur.

(2) Shanghai Cancer Registry

The Shanghai Cancer Registry was established in 1963. It is a centralized population-based cancer registry, which is operated by the Department of Epidemiology of the Shanghai Cancer Institute. The registry was started as a result of regulation on cancer notification issued by the Shanghai Municipal Bureau of Public Health. According to this regulation, each medical facility in Shanghai has the responsibility of reporting all new cases, after admission of cancer patients to hospital either as in-patients or out-patients. Notification forms completed by physicians or medical clerks are forwarded to the cancer registry.

Registry staff then check each notification for errors and completeness, pick out notifications of cancer patients who reside outside the territory of Shanghai, and compile an index card based on the name of the patient. Using these cards, the registry staff can determine whether a newly notified patient has already appeared in the registry records, so as to avoid duplication. There is an average interval of 8 months between diagnosis and notification to the registry.

The cancer registry receives monthly notification of all cancer deaths from the Vital Statistics Units and these death notices are collated with the index cards kept in the registry. Through this system it is estimated that about 15-18% of cases are missed through the passive notification system used by the registry.

The registry staff members periodically (once or twice annually) visit the medical facilities reponsible for reporting new cases and discuss problems and methods for improving the quality of reporting.

Shanghai is the largest city in China with about 10 million residents and incidence data from the Shanghai Cancer Registry is the only incidence data from China included in Cancer Incidence in Five Continents.(21) The overall cancer rate in Shanghai males is about 20% lower than males in Hong Kong but 20% higher than Chinese males in Hawaii, further suggesting that the registration in Shanghai is reasonably complete. The registry sorts cancers by district, so that incident cancer cases among cohort members can be readily identified.

(3) Annual Recontact of Cohort

As a final means of maximizing identification of new cancers among cohort members and of minimizing losses to follow-up, we will attempt to recontact each cohort member on an annual basis, beginning in 1987-88 at the completion of the initial sampling. This will be accomplished by retired nurses, who will visit the last known address of each living cohort member and record details of the interim health history of the cohort member (follow-up questionnaire attached, see Appendix D). For cohort members who have moved, information will be sought on new address from relatives or neighbors; for individuals who have returned to rural areas for retirement, information on health status will be sought from remaining relatives. For persons who cannot be located by this method, we will attempt to obtain residence and health-related information from the local police department.

When a cancer history is elicited from living cohort members or from relatives of dead or permanently relocated cohort members, this information will be matched against data obtained from the death notification and cancer registration system. If the cancer case has not been documented, an attempt will be made to obtain details of the diagnosis from appropriate medical facilities.

Laboratory Methods

(1) Serum Retinol, Beta and Alpha Carotene, and Ascorbic Acid

Retinol and carotenes will be analyzed by a newly developed high performance liquid chromatography method developed by Drs. CS Yang and Kenneth Miller of the Department of Biochemistry, New Jersey Medical School.(Appendix F, 56,66) A 0.1ml serum sample previously stored at -70oC is added to an internal standard (alpha-tocopheryl acetate), mixed with 0.1ml ethanol, and extracted with 0.23 ml hexane. The hexane phase is removed and dried under N2 and the residue dissolved

in 50ml ethanol. A 40ml sample is injected onto a Radial-Pak C18 column and eluted with an isocratic solvent system of methanol-acetinitrile-chloroform (25:60:15) at a flow rate of 1.5ml/minute. The retinol and carotenes are detected by a Waters model 440 absorbance detector with a 280nm filter for the first 8.8 minutes (for retinol) and a 436nm filter for the remainder of the run (for carotenoids). Quantitation is made on the basis of peak area ratios.(66)

This HPLC method is more specific and less tedious than the previously used colorimetric method.(67) In addition it requires only a small sample and allows the determination of specific carotenes rather than a mixture of total carotenoids.

Instability of serum vitamin C is a major concern. When samples are stored at relatively high temperatures (e.g. -20oC) it is widely recommended that samples be acidified with trichloroacetic acid (TCA) for ascorbic acid assays.(68) Ascorbic acid is more stable in acid solution due to the decreased tendency for hydrolysis of the lactone ring at decreased pH. However, if samples are rapidly processed and stored at low temperatures (-70oC), non-stabilized samples show no evidence of a decline in vitamin C concentration for at least a month after collection.(68) (Unfortunately data on longer storage at low temperatures appears to be unavailable). In fact, samples stabilized with TCA and stored at -70oC show a slight upward drift in vitamin C levels, possibly due to formation of spurious sugar compounds which react non-specifically with test reagents (e.g., 2-4 DNPH, see below). We will monitor the differences in ascorbic acid levels after long term storage in acidified versus non-acidified samples (see below)

Ascorbate will be determined by the method of Roe and Kuether (69) as modified by Lowry.(70) After thawing, the serum is agitated to precipitate protein prior to centrifugation for 10 minutes, and to 150ml of the clarified supernatant solution is added 50ml of a 2-4 dinitrophenylhydrazine (2,4-DNPH) - thiourea-copper sulfate reagent and the mixture is agitated on a vortex mixer for 15/sec. The solution is next incubated in a water bath for 3 hours at 37o. At the end of the incubation period, the solution is cooled in an ice bath and 250ml of ice-cold 65% H_2SO_4 is added, followed by thorough mixing.

After standing at room temperature for 30 minutes, absorbances are determined at 520nm using standards ranging from 0 to 20mg/ml.

An additional concern regarding serum vitamin C assays is that levels of water soluble vitamins reflect only immediate diet, and may provide no meaningful information on the usual nutritional status of the patient. Nonetheless, we think such samples will be a useful adjunct to the information provided by the dietary history.

(2) HBsAg

HBsAg will be measured by standard radioimmunoassay methodology using reagent kits from Abbott Laboratories (Ausria II, Abbott Laboratories, North Chicago, Illinois).

(3) Urinary Sodium and Creatinine

Urinary sodium and creatinine will be measured by standard methods (71,72). Using a Beckman Astra, sodium is measured by ion selective electrodes and creatinine by the kinetic alkaline picrate method, using one of the 8cc urine samples stored at -20oC.

(4) Urinary Nitrate and Nitrosamines

Urinary N-nitrosoproline, and N-nitrososarcosine will be analyzed by the method of Wang, using ethyl acetate as the extraction solvent.(73) Drs. Gao and Tu will arrange for training with Dr. Lu at the Chinese Academy of Medical Sciences in Beijing on the methodology of this assay. A 15 ml aliquot of urine, to which N-nitrosopipecolic acid (NPIC) has been added as an internal standard, will be extracted 3 times with 25ml ethyl acetate in the presence of 5g NaCl and 3ml of a 20% ammonium sulfumate solution in 3.6 N H2SO4 (AS solution)and evaporated to dryness in a rotary evaporator at 50oC. Two ml of diethyl ether will be added to the residue, and the samples derivatized with excess diazomethane. After concentration of the derivatized etherial solution to about 0.5ml, a 10ml aliquot will be analyzed by gas chomatography-thermal energy analyzer under appropriate conditions.(74)

Urinary N-nitrosothiazolidine 4-carboxylic acid and N-nitroso-2-methylthiazolidine 4-carboxylic acid will be analyzed by a modified extraction method, using a methanol- dichloromethane mixture as extraction solvent.(74) 7.5 ml of urine will be extracted three times with 2ml methanol- dichloremethane mixture in the presence of NPIC, 2.5g NaCl, and 2ml AS solution. The combined extracts will then be dried and evaporated at 30oC. The residue will be derivatized and analyzed as above. Nitrate will be determined by the method of Sen and Donaldson.(75)

Urinary N-nitrosamino acids and nitrates are stable under storage at -20oC for long periods, with no appreciable artefact formation or degradation of compounds.(73)

To correct for individual differences in volume, creatinine will be measured in all samples.

(5) Urinary Aflatoxin

Techniques available for measuring aflatoxin metabolites in urine were recently reviewed in an IARC Technical Report.(76) The importance of measuring creatinine to correct for individual differences in volume when conducting field studies in which aflatoxin concentration is measured in single void urines was stressed in this report. It was also generally agreed by participants in this conference that urine samples should be stored cold and protected from light. All of these precautions have been taken in the study proposed here.

In this study, a Sep-pak C18 reversed phase cartridge has been used to concentrate aflatoxin metabolites in the urine samples. The description for preparing and using the Sep-pak cartridges for urine separation has been described above.

Our technique is an enzyme-linked immunoassay to aflatoxin B1-modified DNA. Details of the development and methodology of this assay can be found in the MIT subcontract (see Appendix G), and in the attached references, Appendix F.

One limitation of this method (and other available methods) is that only recent aflatoxin exposure can be determined, so that one must assume that recent diet (and exposure to aflatoxins) is related on a population basis to usual diet (and exposure to aflaxtoxins).

(6) Long Term Storage

Possible deterioration of nutrients and other compounds of interest after longterm storage is of some concern to us. While we cannot control deterioration, we can at least measure it. Therefore, we will collect pooled serum and urine samples from four groups of five Shanghai Cancer Institute workers, which we will process and store in a manner identical to that for the study participants. We will store pooled non-acidified serum samples at -70oC as well as pooled serum samples acidified with 10% trichloroacetic acid. We will test these samples immediately and at one month intervals for the first six months to monitor differences between acidified and non-acidified samples stored for long periods at low temperatures. We will then test the four pooled serum samples on an annual basis for HBsAg, carotenes, retinol, and ascorbic acid (acidified and non-acidified) and the four pooled urines for sodium, creatinine, aflatoxins, nitrate, and nitrosamines.

Time Schedule of Laboratory Testing

All laboratory tests, with the exception of urinary aflatoxin assay, will be performed in Shanghai. We propose to perform all laboratory tests on approximately 10% of the cohort (1800 individuals) over a 3-year period beginning at the end of year 2 of the grant. The 10% sample of cohort members will be generated by the USC computer as a stratified random sample which is frequency matched in age to the total expected cases of liver, stomach, lung and esophageal cancers. Every four months beginning in March, 1988 (two months following completion of the initial sampling of the cohort), all laboratory assays described in this proposal will be performed on 10% of the stratified sample of cohort members (in other words, 1% of the entire cohort). Concurrent with the testing of this 1% cohort sample, all cases of liver, stomach, lung and esophageal cancers that have been identified and not yet tested will have selected laboratory assays performed on their specimens. That is, serum HBsAg and urinary aflatoxin will be measured on HCC cases; urinary sodium and creatinine will be measured on stomach cancer cases; ascorbic acid, and urinary nitrate and nitrosamines will be measured on stomach and esophageal

cancer cases; and serum retinol, and carotenes will be measured in stomach, lung and esophageal cancer cases. Therefore, every four months we will test 1% of the cohort together with all cases of liver, stomach, lung, and esophageal cancer that have been identified during the previous four months. At the end of the grant period 10% of the cohort will have all laboratoary measurements completed and all cases of liver, stomach, lung and esophageal cancer will have had selected laboratory assays completed. Our proposed approach has the following appeals: (1) Cases and non-cases will be tested concurrently such that possible deterioration of the biologic specimens and drift in the laboratory assays can be studied and controlled for if necessary; (2) A minimum number of laboratory technicians will be hired such that inter-technician variation would be minimized; and (3) Specimens on 90% of the cohort will still be available at the end of 5 years for studying other diseases and exposures. A 10% sample will provide adequate power to study associations between diseases and exposures of primary concern to us (see sample size considerations below).

Sample Size Considerations

Based on age-and site-specific incidence data from the Shanghai Cancer Registry and assuming a final sample size of about 18,000 persons, we expect 165 lung, 153 stomach, 91 primary liver, and 60 esophageal cancer cases to be diagnosed among cohort members by the end of the grant period. These cases will be compared to approximately 1800 members of the cohort (10% sample), more than 10 times the expected number of any given cancer under study. For comparison purposes, the following table shows the expected power of a study with a 10 to 1 control to case ratio to detect RRs of 2.0 and 5.0 for a wide range of prevalence values, assuming a one-sided significance level of 0.05.

Table 3
Expected power of study, one-sided significance level = 0.05

Prevalence of Exposure	10%	25%	50%	75%
RR=2.0				
Lung	0.88	1.00	1.00	0.94
Stomach	0.86	0.98	0.99	0.93
Liver	0.68	0.89	0.91	0.73
Esophagus	0.53	0.74	0.76	0.52
RR=5.0				
Lung	1.00	1.00	1.00	1.00
Stomach	1.00	1.00	1.00	1.00
Liver	1.00	1.00	1.00	1.00
Esophagus	1.00	1.00	1.00	0.99

Based on our previous studies on Shanghai middle-aged males, we expect the following prevalence rates for several study factors of interest:

Current smokers	75%
Daily drinkers	25%
HBsAg positivity	22%

From previous studies by us and others, we estimate the following relative risks for these study factors with the relevant cancers of interest:

	RR
Liver Cancer	
HBsAg positivity	40.0
Lung Cancer	
Current smoker	10.0
Esophageal Cancer	
Current smoker	5.0
Daily drinker	10.0

Therefore, this study is almost certain to detect significant effects of hepatitis B antigenemia and primary liver cancer, cigarette smoking and lung cancer, and cigarette smoking and alcohol use and esophageal cancer. The above table shows that the power to detect a RR of 2.0 between individuals with above median values of a given laboratory measurement and those with values below the median will likely be very high for studies of lung, stomach and liver cancer. Furthermore, we will also analyze the laboratory measurements as continuous variables and as ordered categorical variables whose tests are much more sensitive than the median test.

Data Analysis

We will employ regression methods appropriate for a case-cohort design in the analysis of our data (77). The model proposed by Cox (78) will be used in the estimation and significance testing of relative risks associated with various exposure levels. The study variables will be analysed singly and then jointly to examine confounding and interaction effects.

We will also analyze the interview data of the entire cohort. Person-years of observation will be used as denominators in the computation of rates between various subgroups of the cohort.(79) Age-adjusted incidence rates of specific cancers will be compared between individuals with varying exposure levels of single or multiple risk factors. In addition to Cox's model, poisson regression models will be used in the estimation and significance testing of relative risks.(80) Study variables will be examined singly and then jointly for confounding and interaction effects.

E. HUMAN SUBJECTS

To insure security of computer stored information, data will be stored by identification number only. Questionnaires will be stored in locked file cabinets both in Shanghai and at USC. Any published results from the study will be in the form of tabular descriptions of groups only. The minimal risks and discomforts of venipuncture including hematoma and/or fainting will be explained to the patients and a signed informed consent form will be obtained (Appendix C). The characteristics of the proposal study population is described in detail above. Study participants will derive no immediate benefit but

this study should prove beneficial to society by improving our understanding of the etiology of liver, stomach, lung and esophageal cancers.

The risks to subjects in this study are minimal, since participation requires only the completion of a brief in person interview and provision of a small blood and urine sample. The Shanghai Cancer Institute has assembled an ad hoc review committee, set up in accordance with guidelines established by the US National Institutes of Health, for assuring protection of human subjects for research conducted in collaboration with US scientists. The make-up of this committee and the adequency of its review procedures have already been found acceptable for a research contract between the National Cancer Institute and the Shanghai Cancer Institute (RF#NOI-CP-21012), a study also involving in person interviewing and collection of blood samples for epidemiologic research.

F. VERTEBRATE ANIMALS

None

G. CONSULTANTS

C. S. Yang, Ph.D, of the New Jersey School of Medicine will serve as a consultant on this project. Dr. Yang and his colleague, Dr. Kenneth Miller, have recently developed a method of measuring fat soluble vitamins in serum by high performance liquid chromatography. Dr. Yang will be training Dr. Xu Li-wei from the Shanghai Cancer Institute in the methodology for these assays this winter (1985-86). We think his continued input into the appropriate laboratory arrangements and analysis of serum samples in Shanghai will be invaluable to this study.

H. CONSORTIUM ARRANGEMENTS

The Shanghai Cancer Institute under the direction of Gao Yu-Tang, M.D., will be responsible for the collection of blood and urine samples and dietary histories on 18,000 men ages 45-64, the routine follow-up of these men for cancer occurrence and/or death, and for conducting most of the laboratory assays proposed here: retinol, carotenes, ascorbic acid, HBsAg, urinary sodium/creatinine, urinary nitrosamines and nitrates.

The laboratory of Gerald Wogan, M.D. of the Massachusetts Institute of Technology will conduct urine assays for aflatoxin metabolites.

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RE: Grant Proposal: A Cohort Study of Dietary Factors in the Etiology of Cancer In Shanghai

The appropriate programmatic and administrative personnel of each institution involved in the grant application are aware of the NIH consortium grant policy and are prepared to establish the necessary inter-institutional agreements consist with that policy.

For the University of Southern California:

Cornelius J. Pings
Signature

Cornelius J. Pings
Typed Name

Senior Vice President for Academic Affairs
Title

10/31/85
Date

Ronald K. Ross, M.D.
Principal Investigator

Ronald K Ross
Signature

10/30/85
Date

For the Shanghai Cancer Institute:

Ma ji qing
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Ma Ji-Qing
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Vice Director
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21, October, 1985
Date

Gao Yu-Tong, M.D.
Principal Investigator

Gao Yu Tang
Signature

MD phy 68

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For the University of Southern California:

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Ronald K. Ross, M.D.
Principal Investigator

Ronald K. Ross
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Date

Gerald N. Wogan, M.D.
Principal Investigator

Signature

10/30/85
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☐ ORIGINAL ☒ FOLLOWUP ☐ EXEMPTION (previously undesignated)

☒ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER

☒ New ☐ Competing continuation ☐ Noncompeting continuation ☐ Supplemental

APPLICATION IDENTIFICATION NO. *(if known)*

1 R01 CA43092-01

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an Institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act as implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have an assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

A Cohort Study of Dietary Factors in the Etiology of Cancer in Shanghai

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

Ronald K. Ross, M.D.

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(see reverse side)*

4. HHS ASSURANCE STATUS

☒ This institution has an approved assurance of compliance on file with HHS which covers this activity.

M1372 Assurance identification number 01 IRB identification number

☐ No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

☒ This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. *(See reverse side of this form.)*

1-08-87 Date of IRB review and approval. *(If approval is pending, write "pending." Followup certification is required.)*
(month/day/year)

☒ FullBoard Review ☐ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification *(Form HHS 596)* will be submitted.

☐ Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ *(insert paragraph number of exemption in 46.101(b), 1 through 5)*, but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. University of Southern California Health Sciences Campus 1975 Zonal Avenue, KAM 110 Los Angeles, CA 90033 (213)224-7033	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL *(print or type)* John W. Thurgood, Interim Director Department of Contracts & Grants	NAME AND TITLE OF OFFICIAL *(print or type)*
SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)* John W. Thurgood 1-12-87	SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)*

HHS 596 (Rev. 1/82)

(If additional space is needed, please use reverse side under "Notes.")

2025794695

OMB No. 0925-0337

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☐ ORIGINAL ☒ FOLLOWUP ☐ EXEMPTION (previously undesignated)

☒ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER

☒ New ☐ Competing continuation ☐ Noncompeting continuation ☐ Supplemental

APPLICATION IDENTIFICATION NO. *(if known)*

Assignment No. 1 R01 CA43092-01

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an Institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act as implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have an assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

A Cohort Study of Dietary Factors in the Etiology of Cancer in Shanghai

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

Ronald K. Ross, M.D.

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(see reverse side)*

4. HHS ASSURANCE STATUS

☒ This institution has an approved assurance of compliance on file with HHS which covers this activity.

M1372 Assurance identification number 01 IRB identification number

☐ *No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.*

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

☒ This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. *(See reverse side of this form.)*

12/19/85 Date of IRB review and approval. *(If approval is pending, write "pending." Followup certification is required.)*
(month/day/year)

☐ Full Board Review ☒ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification *(Form HHS 596)* will be submitted.

☐ Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ *(insert paragraph number of exemption in 46.101(b), 1 through 5)*; but the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. University of Southern California University Park Los Angeles, California 90089-1147 (213) 224-7033	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL *(print or type)* William C. Hromadka, Executive Director Department of Contracts and Grants	NAME AND TITLE OF OFFICIAL *(print or type)*
SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)* William C. Hromadka	SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)*

HHS-596 (Rev. 1/82) *(If additional space is needed, please use reverse side under "Notes.")*

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PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: ROSS, Ronald K. AA

CHECKLIST

This is the required last page of the application.

(Check the appropriate boxes and provide the information requested.)

TYPE OF APPLICATION

[X] NEW application *(This application is being submitted to the PHS for the first time.)*

[ ] COMPETING CONTINUATION of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation or supplemental application.)

[ ] Change of Principal Investigator/Program Director.
Name of former Principal Investigator/Program Director: _____

ASSURANCES *(See GENERAL INFORMATION section of instructions.)*

a. Civil Rights	b. Handicapped Individuals	c. Sex Discrimination	d. Vertebrate Animals *(If applicable)*	e. Human Subjects *(If applicable)*
[X] Filed	[X] Filed	[X] Filed	[X] Filed	[X] Filed
[ ] Not filed	[ ] Not filed	[ ] Not filed	[ ] Not filed	[ ] Not filed

INDIRECT COSTS

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates*, and submit it to the appropriate DHHS Regional Office. Indirect costs will not be paid on foreign grants, construction grants, and grants to individuals, and usually not on grants in support of conferences.

[X] DHHS Agreement Dated: 1/14/85

_____ % Salary and Wages *or* 61 (modified) % Total Direct Costs.

Is this an off-site or other special rate, or is more than one rate involved? [X] NO [ ] YES
(If "YES," explain and provide the basis for the indirect cost calculation.)

[ ] DHHS Agreement being negotiated with _____ Regional Office.

[ ] No DHHS Agreement, but rate established with _____ Date _____

[ ] No Indirect Costs Requested.

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